NAPHTHYRIDINE ANTIMALARIAL AGENTS

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Exxon Research and Engineering Company

Prepared for:

Army Medical Research and Development Command

June 1974

Unclassified

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

REPORT DOCUMENTATION PAGE		READ INSTRUCTIONS BEFORE COMPLETING FORM
1. REPORT NUMBER	2. GOVT ACCESSION NO.	3. RECIPIENT'S CATALOG NUMBER AD-784 627
4. TITLE (and Subtitle) Naphthyridine Antimalarial Agents		5. TYPE OF REPORT & PERIOD COVERED Annual Report April 1, 1973-March 31, 1974
		6. PERFORMING ORG. REPORT NUMBER GRU.5BJ.JB.74
7. AUTHOR(s) John F. Pilot		8. CONTRACT OR GRANT NUMBER(s) Contract DADA 17-73-C-3079
9. PERFORMING ORGANIZATION NAME AND ADDRESS Exxon Research and Engineering Company Government Research Laboratory P.O. Box 8, Linden, New Jersey 07036		10. PROGRAM ELEMENT PROJECT, TASK AREA & WORK UNIT NUMBERS
11. CONTROLLING OFFICE NAME AND ADDRESS U.S. Army Medical Research and Develcpment Command Washington, D.C. 20314		12. REPORT DATE June 1974
		13. NUMBER OF PAGES 190
14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office)		15. SECURITY CLASS (of this report) Unclassified
		15a. DECLASSIFICATION/DOWNGRADING SCHEDULE

16. DISTRIBUTION STATEMENT (of this Report)

Approved for public release; distribution unlimited.

17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)

18. SUPPLEMENTARY NOTES

None

19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

Antimalarial

Naphthyridine

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

Interest in the 4-amino-1,5-naphthyridines as potential prophylactic antimalarial agents has been generated by the structural similarity of this ring system to both the 4- and 8-aminoquinolines. In our synthetic studies of this year, we sought to expand upon the derivatives of 4-amino-1,5-naphthyridine which are currently available in an effort to secure an optimal prophylactic antimalarial drug. Accordingly, as a result of our synthetic efforts, a total of

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one-hundred and three compounds comprising nineteen 1,5-naphthyridine target derivatives, forty-one 1,5-naphthyridine intermediates, and forty-three miscellaneous precursors have been prepared and submitted for biologic testing.

In our synthetic studies for this year, we have been mainly concerned with the formation of three main classes of target structures. These have included the 6-alkoxy-, 2-alkoxy-, and 2,6-dialkoxy-4-amino-1,5-naphthyridines. The significant results of our synthetic studies include: the improvization of a new synthetic route for the preparation of 6-alkoxy-4-amino-1,5-naphthyridines which are not attainable via the conventional techniques; the development of a new procedure to incorporate the pentaquine side chain onto the 2- and 6-alkoxy-4-amino-1,5-naphthyridines; the synthesis of a variety of 6-alkoxy-3-carboalkoxy-4-hydroxy-1,5-naphthyridines for inclusion in the WRAIR screening program; and the preparation of 2-methoxy-, 2-hydroxy-, 6-methoxy-, 6-ethoxy-, 6-n-butoxy-, and 6-(2,2,2-trifluoroethoxy)-1,5-naphthyridines bearing both the pentaquine and pamaquine side chains on the ring-4 position.

While full biologic testing data are not yet available, test results obtained on most of the target drugs submitted to WRAIR have disclosed no significant prophylactic activity in the lower dosage range (1 mg/kg). However, one of the target drugs, 2-hydroxy-4-(5-isopropyl-amino pentylamino)-1,5-naphthyridine, continues to afford protection after seventy days at a dosage level of 10 mg/kg.

GRU.5BJJB.74

NAPHTHYRIDINE ANTIMALARIAL AGENTS

Annual Technical Report

for

April 1, 1973 - March 31, 1974

by

John F. Pilot
(201-474-3962)

June, 1974

Supported by

U.S. Army Medical Research and Development Command
Washington, D.C. 20314

Contract No. DADA17-73-C-3079

Exxon Research and Engineering Company
Government Research Laboratory
Linden, New Jersey 07036

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1. SUMMARY

Interest in the 4-amino-1,5-naphthyridines as potential prophylactic antimalarial agents has been generated by the structural similarity of this ring system to both the 4- and 8-aminoquinolines. In our synthetic studies for this year, we sought to expand upon the derivatives of 4-amino-1,5-naphthyridine which are currently available in an effort to secure an optimal prophylactic antimalarial drug. Accordingly, as a result of our synthetic efforts, a total of one-hundred and three compounds comprising nineteen 1,5-naphthyridine target derivatives, forty-one 1,5-naphthyridine intermediates, and forty-three miscellaneous precursors have been prepared and submitted for biologic testing.

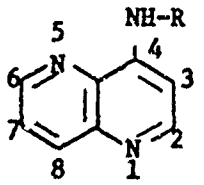
In our synthetic studies for this year, we have been mainly concerned with the formation of three main classes of target structures. These have included the 6-alkoxy-, 2-alkoxy, and 2,6-dialkoxy-4-amino-1,5-naphthyridines. The significant results of our synthetic studies include: the improvization of a new synthetic route for the preparation of 6-alkoxy-4-amino-1,5-naphthyridines which are not attainble via the conventional techniques; the development of a new procedure to incorporate the pentaquine side chain onto the 2- and 6-alkoxy-4-amino-1,5-naphthyridines; the synthesis of a variety of 6-alkoxy-3-carboalkoxy-4-hydroxy-1,5-naphthyridines for inclusion in the WRAIR screening program; and the preparation of 2-methoxy-, 2-hydroxy-, 6-methoxy-, 6-ethoxy-, 6-n-butoxy-, and 6-(2,2,2-trifluoroethoxy)-1,5-naphthyridines bearing both the pentaquine and pamaquine side chains on the ring-4 position.

While full biologic testing data are not yet available, test results obtained on most of the target drugs submitted to WRAIR have disclosed no significant prophylactic activity in the lower dosage range (1 mg/kg). However, one of the target drugs, 2-hydroxy-4-(5-isopropylaminopentylamino)-1,5-naphthyridine, continues to afford protection after seventy days at a dosage level of 10 mg/kg.

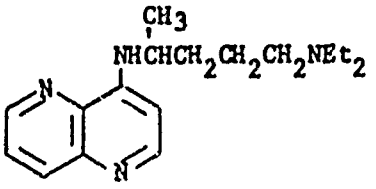
2. INTRODUCTION

The drugs presently available for the treatment of malaria suffer from two serious deficiencies. First, no single agent is suitable for all purposes. Secondly, drug resistant strains of the parasite have evolved in the early 1960's. Clearly, further developments in drug design must lead to agents which possess pharmacologic and chemotherapeutic properties which are superior to those presently available. The goals of new synthetic efforts must be directed toward the development of agents which exhibit broad activity against all life cycles of the parasite. In addition, they should possess high potency, low toxicity, and a long duration of activity. Ideally, a prophylactic drug is sought for the recently encountered drug resistant stains of the malaria parasite.

With all of the above in mind, it is our contention that certain 4-amino-1,5-naphthyridines,



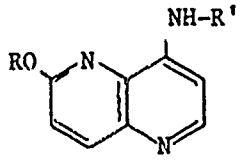
should possess the desired prophylactic characteristics. Quinine, a classic example of a specific chemotheraupeutic agent, incorporates a quinoline ring as a basic structural fragment. The quinoline nucleus has, therefore, served as a template for biochemists in the design of a wide array of candidate antimalarial drugs. Of the many substituent variations effected upon the quinoline nucleus, the 4-amino and 8-amino substituted analogs have exhibited the greatest activity (1). In general, the 4-aminoquinolines, e.g., chloroquine, are schinzontocidal agents which act at the asexual erythrocytic life cycle of the malaria parasite. By contrast, the 8-aminoquinolines, as typified by pamaquine, are gametocytocidal drugs which act against the secondary exoerythrocytic stages and thereby destroy the sexual forms of the human malaria parasite (2). Derivatives of the 4-amino-1,5-naphthyridines should, therefore, exhibit an enhanced antimalarial activity, since they are isosteres of both the 4- and 8-aminoquinolines. This supposition has been confirmed by an early report in the literature that 4-(4-diethylamino-1-methylbutylamino)-1,5-naphthyridine,



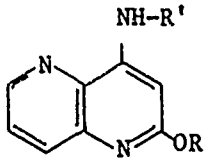
was found to exhibit an antimalarial activity comparable to quinine itself (3,4). Moreover, recent reports in the literature have disclosed significant antimalarial activity for the 4-amino-1,5-naphthyridines which are substituted with alkoxy groups in both the 2- and 6-positions (2,5). In our research, we sought to expand upon the derivatives of 4-amino-1,5-naphthyridine currently available in an effort to produce an optimum drug. The results of our synthetic studies for this year are fully discussed in the text of this report.

3. SYNTHESIS-RESULTS AND DISCUSSION

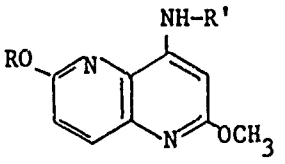
Our synthetic efforts for this year have been concentrated on the preparation of the target 6-alkoxy (A), 2-alkoxy (B), and 2,6-dialkoxy-4-amino-1,5-naphthyridine analogs (C) shown below.



(A)

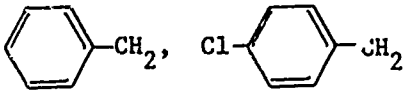


(B)



(C)

R = CH_3, CH_3CH_2, $CH_3(CH_2)_3$, $CH_3(CH_2)_9$, CF_3CH_2,



R' = $-CH(CH_3)(CH_2)_3NEt_2$ (Pamaquine Side Chain)

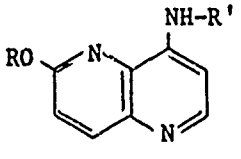
$-(CH_2)_5NHCH(CH_3)_2$ (Pentaquine Side Chain)

$-CH(CH_3)(CH_2)_3NH_2$ (Primaquine Side Chain)

In the three main subsections below, we have described the synthetic progress attained this year with respect to the preparation of these three general classes of candidate antimalarial drugs.

3.1 6-Alkoxy-4-Amino-1,5-Naphthyridines

In the course of our synthetic studies in the title area for this year, we have prepared target derivatives of the following general structure.



R = CH_3, CH_3CH_2, $CH_3(CH_2)_3$, CF_3CH_2

R' = $CH(CH_3)(CH_2)_3NEt_2$, $(CH_2)_5NHCH(CH_3)_2$

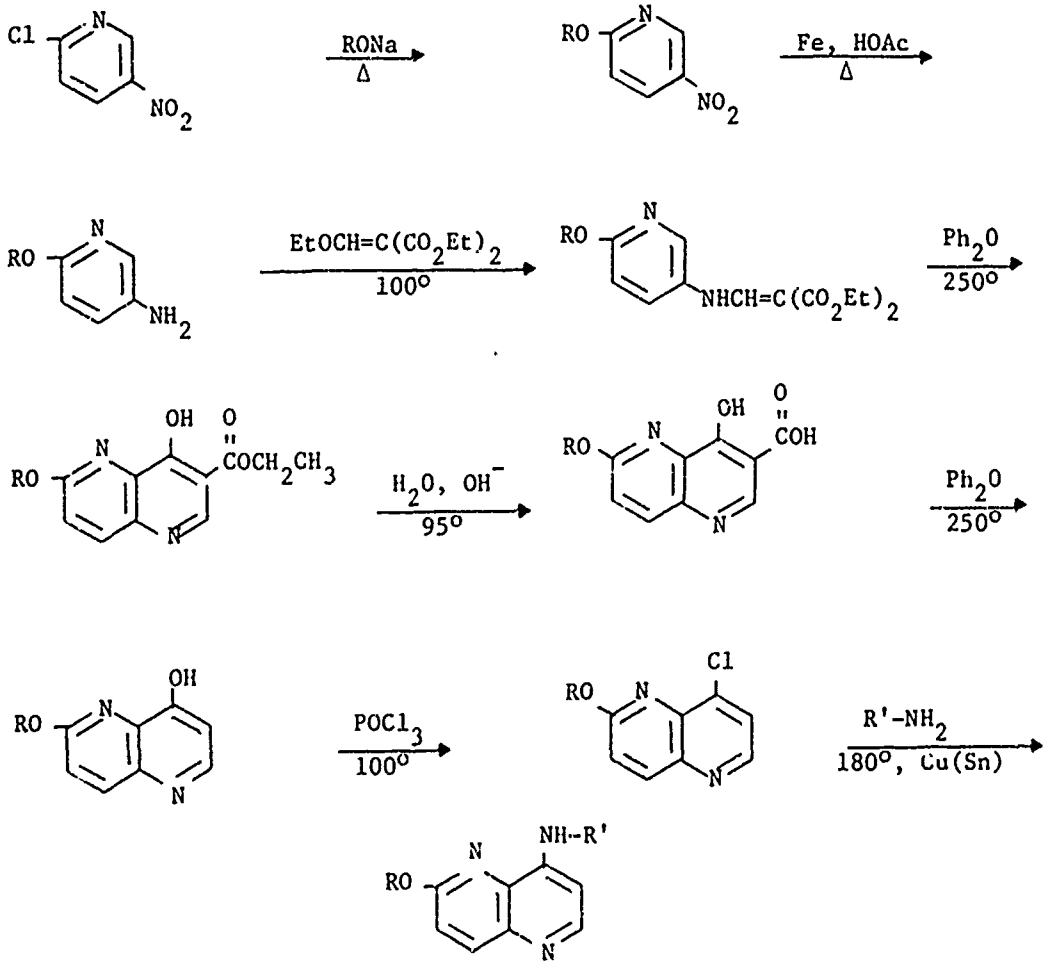
Two basic synthetic routes were employed to prepare the target derivatives depicted above. The first, the classical ethoxymethylenemalonic ester (EMME) procedure, is explained in Section 3.1.1 immediately below. The second synthetic route, a modified EMME procedure, is fully discussed in Section 3.1.2, and has afforded target structures which were unattainable via the conventional EMME technique. Finally, in Section 3.1.3 we have included a discussion of the preparative chemistry of a 6-alkoxy-3-carboalkoxy-4-hydroxy-1,5-naphthyridine specifically requested by WRAIR personnel.

3.1.1 Conventional EMME Procedure

The title synthetic route to the target 6-alkoxy-4-amino-1,5-naphthyridines is based upon the highly established ethoxymethylenemalonic ester (EMME) procedure which has been successfully applied for the formation of a vast number of quinoline antimalarials (6). Goldberg was the first to apply this procedure for the formation of 6-alkoxy-4-amino-1,5-naphthyridines (5). The essential features of this synthetic procedure are outlined in Scheme 1 below.

Scheme 1

Conventional EMME Route to 6-Alkoxy Analogs

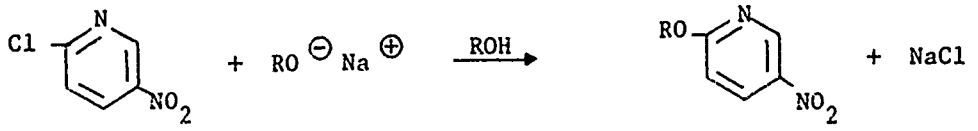


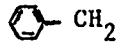
In the following subsections, we have fully delineated a description of the preparative chemistry of each of the precursors, intermediates, and target derivatives prepared this year in accord with Scheme 1.

2-Alkoxy-5-Nitropyridines

The 2-alkoxy-5-nitropyridines which were prepared this year are included in Table 1 at the end of this section along with their physical constants and full analytical data.

The 2-ethoxy-, 2-n-butoxy-, 2-n-decyloxy-, 2-(2,2,2-trifluoroethoxy)-, and 2-benzyloxy-5-nitropyridines were prepared by analogy to the general procedure as reported by Friedman (7).



R = CH_3CH_2, $CH_3(CH_2)_3$, $CH_3(CH_2)_9$, CF_3CH_2,  CH_2

In essence, the appropriate sodium alcoholate was prepared in situ, and the commercially available 2-chloro-5-nitropyridine added as a solid at room temperature. The reaction was then driven to completion by heating to 65-85° for several hours. After filtration of the sodium chloride, solvent was removed under reduced pressure to afford the crude 2-alkoxy-5-nitropyridines. Pure 2-n-butoxy-5-nitropyridine was obtained in high yield by vacuum distillation. The remaining 2-alkoxy-5-nitropyridines were obtained as analytically pure solids by recrystallization of the crude residua from warm methanol. The infrared spectrum of 2-n-decyloxy-5-nitropyridine (Figure 1) is representative of this group and exhibits the appropriate aromatic nitro group absorptions near 6.5 and 7.5 μ (8).

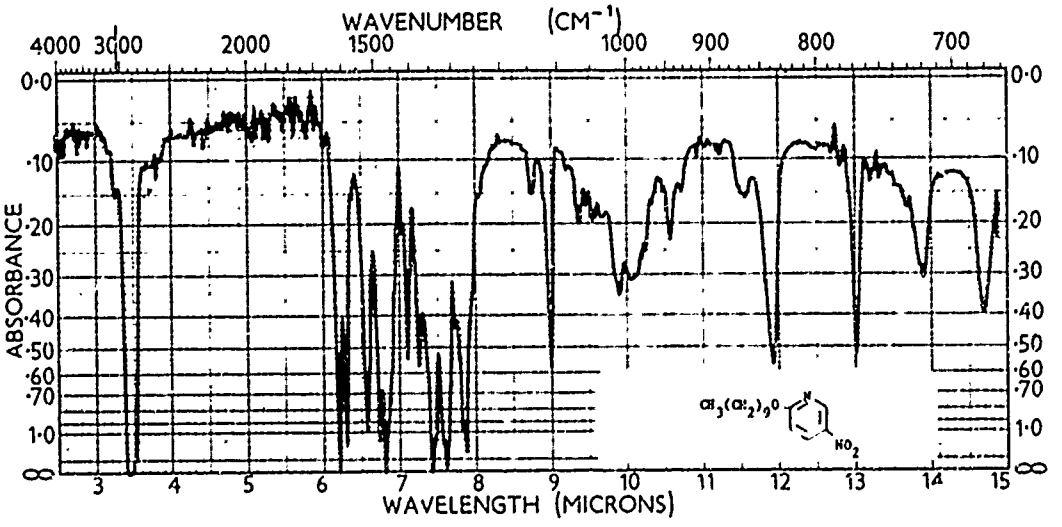
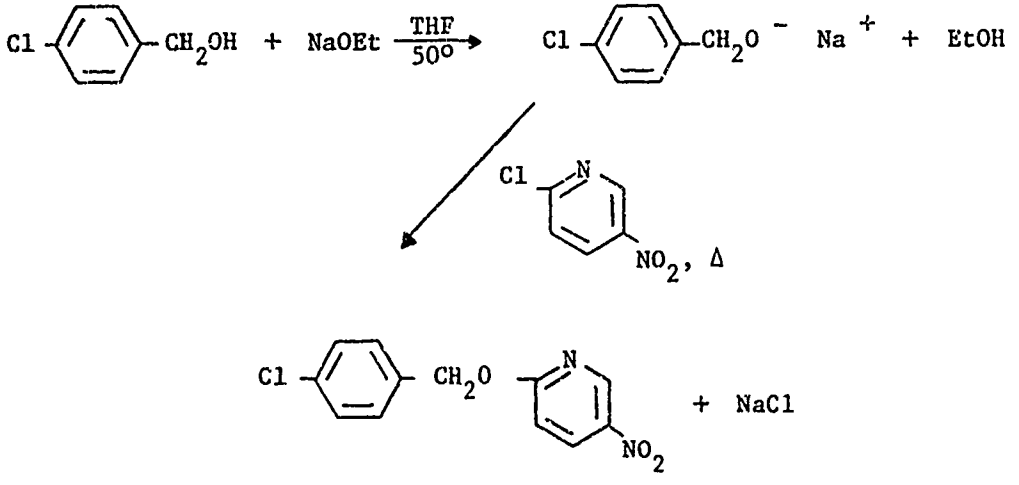


Figure 1. Infrared spectrum of 2-n-decyloxy-5-nitropyridine (nujol mull).

The preparation of 2-(p-chlorobenzyloxy)-5-nitropyridine initially presented some synthetic difficulties. Preparation of the sodium salt of p-chlorobenzyl alcohol in refluxing toluene solution, followed by the addition of 2-chloro-5-nitropyridine did not lead to product formation even when refluxed for several days. Presumably, self-condensation of p-chlorobenzyl alcohol was effected during the formation of its sodium salt. Also, no product was observed in the reactions of p-chlorobenzyl alcohol itself with 2-chloro-5-nitropyridine in either refluxing tetrahydrofuran or methanol solution, and with or without sodium methoxide as catalyst. An attempt to generate the sodium salt of p-chlorobenzyl alcohol by the addition of this alcohol to one mole-equivalent of sodium methoxide in methanol was unsuccessfull. The addition of 2-chloro-5-nitropyridine to this mixture lead to a nearly quantitative yield of 2-methoxy-5-nitropyridine (NP-1) after the usual work-up.

The preparation of the desired 2-(p-chlorobenzyloxy)-5-nitropyridine was finally effected according to the following procedure. Solid p-chlorobenzyl alcohol was added portionwise to a suspension of sodium ethoxide in tetrahydrofuran at room temperature. The metathetical reaction was completed by slowly heating this mixture to 50° and maintaining this temperature for several hours. Solid 2-chloro-5-nitropyridine was then added portionwise at room temperature, and the mixture refluxed for about three hours.



After filtration of the sodium chloride, an excess of methanol was added to the THF filtrate, and 2-(p-chlorobenzyloxy)-5-nitropyridine separated from solution as a light tan powder in ca., 24% yield. The analytical sample (Table 1) was obtained as a colorless solid from methanol-charcoal. The proton spectrum is reproduced in Figure 2 and is clearly in accord with the structure as formulated. The following peak assignments have been made:

0.92τ (1H, d, ring H-6); 1.65τ (1H, q, ring H-4); 2.63τ (4H, s, p-Cl ring); 3.14τ (1H, d, ring H-3); 4.55τ (2H, s, OCH_2); $J_{3,4}$ = 9.0 Hz; and $J_{4,6}$ = 2.9 Hz.

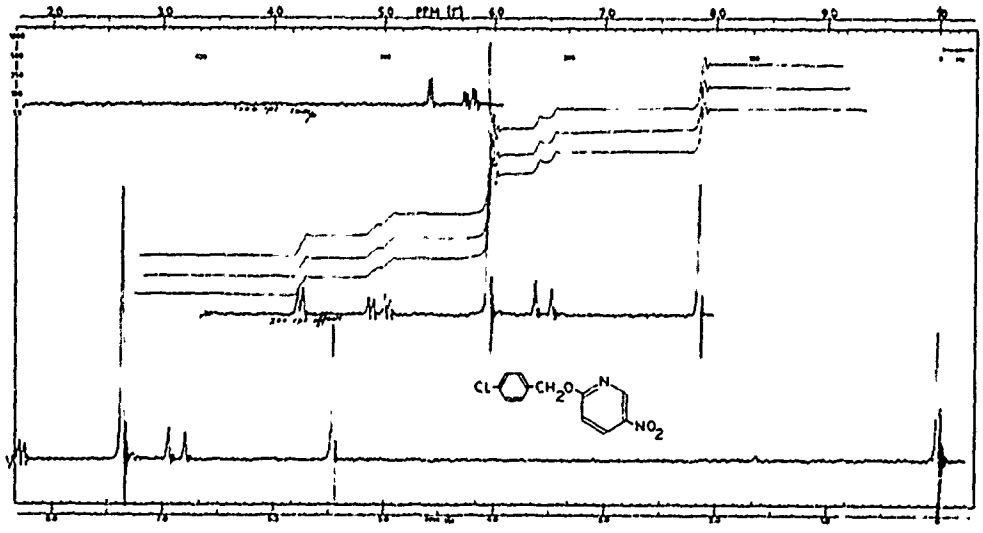


Figure 2. Proton spectrum of 2-(p-chlorobenzyloxy)-5-nitropyridine ($CDCl_3$).

Table 1

2-Alkoxy-5-Nitropyridines

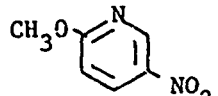
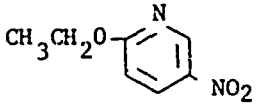
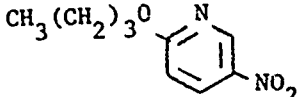
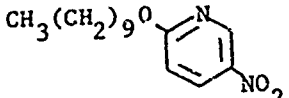
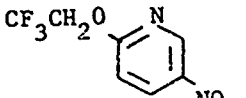
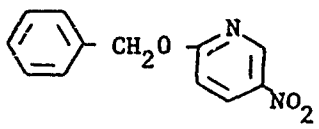
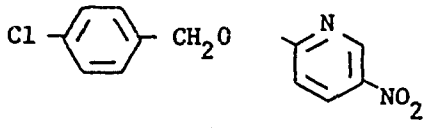
Structure	M.P., °C B.P., °C(mm)	Elemental Analysis C	 H	 N	
 (NP-1)	107-108	46.75 46.63	3.93 3.92	18.18 18.15	Theory Found
 (NP-18)	91-92	50.00 49.93	4.79 4.75	16.66 16.47	
 (NP-2)	114-115 (1.5)	55.09 55.05	6.17 5.90	14.28 14.17	
 (NP-3)	33-34	64.26 64.50	8.63 8.56	9.99 10.01	
 (NP-4)	35-36	37.85 37.62	2.27 2.28	12.61 12.80	

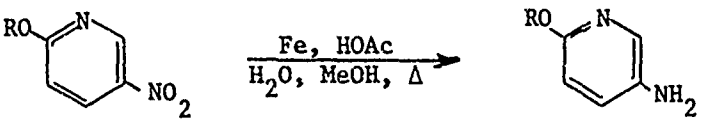
Table 1 (Cont'd.)

Structure	M.P., °C B.P., °C(mm)	Elemental Analysis C	 H	 N
 (NP-41)	105–106	62.60 63.00	4.38 4.43	12.17 12.37
 (NP-5)	134–135	54.45 54.57	3.43 3.34	10.59[(a)] 10.63

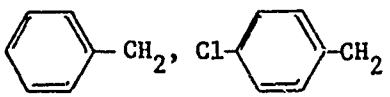
(a) Theory for Cl = 13.40; Found = 13.45

5-Amino-2-Alkoxypyridine

5-Amino-2-methoxypyridine was commercially available and was used as received. Each of the six remaining 2-alkoxy-5-nitropyridines were conveniently reduced to the corresponding amine employing iron and acetic acid in refluxing methanol-water solution.



R = CH_3CH_2, $CH_3(CH_2)_3$, $CH_3(CH_2)_9$, CF_3CH_2,



This general procedure was reported by Friedman (7), and worked well in each case. Completion of the reaction was conveniently monitored by a change in the reaction mixture color from brown-gray to a deep black. After work-up (see experimental) the ethoxy analog was judged to be sufficiently pure for the next step and was used crude. The n-butoxy and n-decyloxy derivatives were characterized as their dihydrochlorides (Table 2), and the analytical data for the other free bases are also included in Table 2. The proton spectra for the 2,2,2-trifluoroethoxy and p-chlorobenzyloxy analogs are reproduced in Figures 3 and 4, respectively.

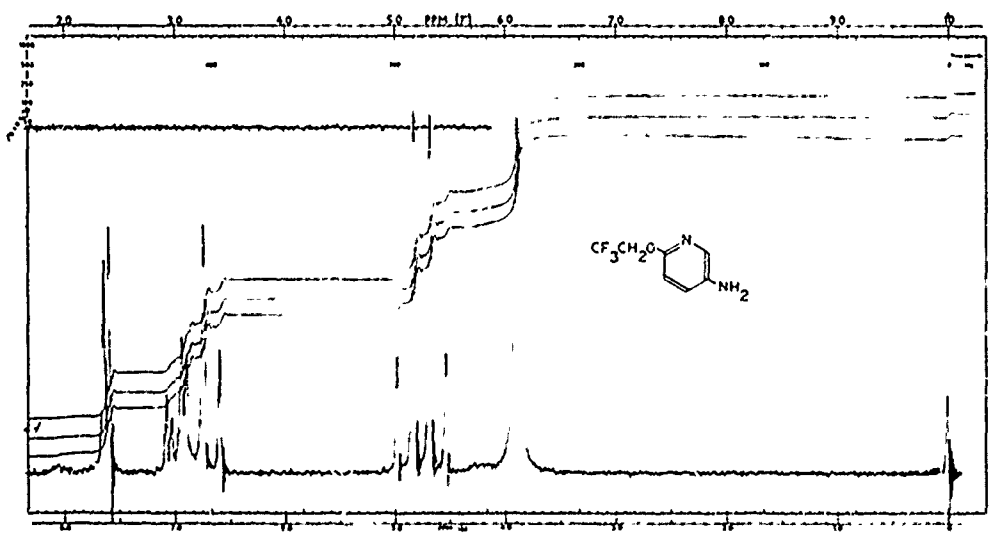


Figure 3. Proton spectrum of 5-amino-2-(2,2,2-trifluoroethoxy)pyridine (neat)

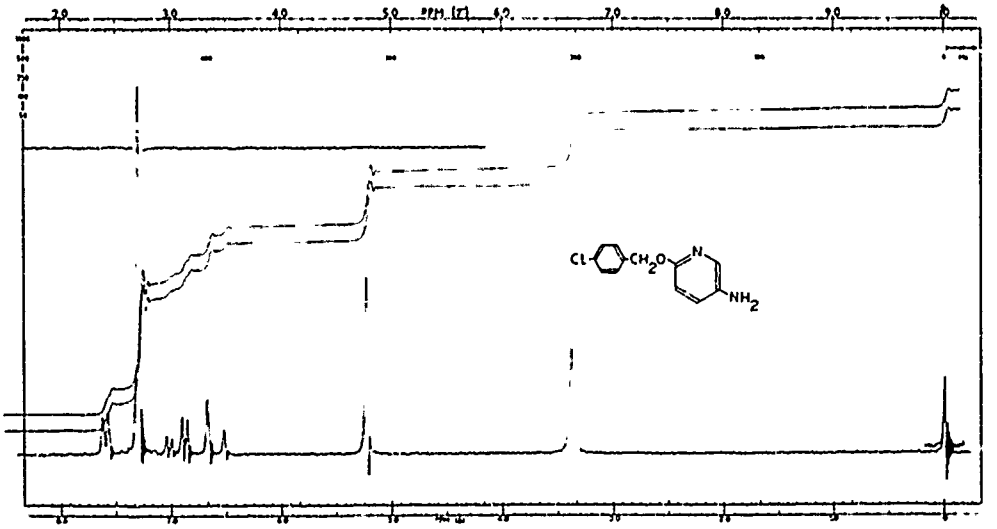
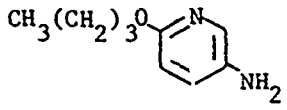
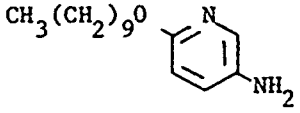
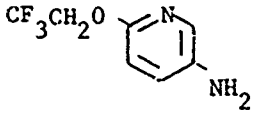
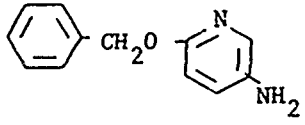
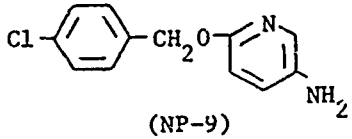


Figure 4. Proton spectrum of 5-amino-2-(p-chlorobenzyloxy)pyridine ($CDCl_3$)

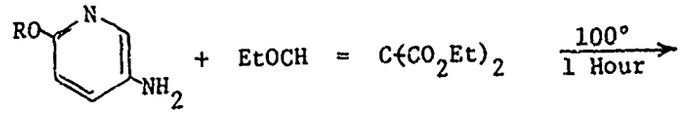
Table 2

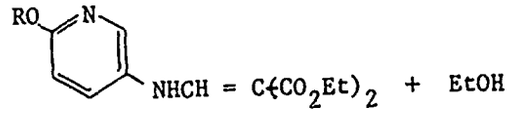
5-Amino-2-Alkoxypyridines

Structure	M.P., °C B.P., °C(mm)	Elemental Analysis C	 H	 N	
 · 2 HCl (NP-6)	137-139	45.20 45.37	6.74 6.70	11.72 11.83	Theory Found
 (NP-7)	118-120	55.72 56.01	8.73 8.71	8.67 8.75	
 (NP-8)	86-87 (2.0)	43.75 43.75	3.67 3.53	14.58 14.56	
 (NP-42)	40.5-41.0	71.97 71.92	6.04 6.13	13.99 14.00	
 (NP-9)	89-90	61.41 61.82	4.73 4.79	11.94 12.02	

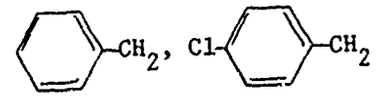
6-Alkoxy-2-Pyridylaminomethylenemalonates

The title derivatives which were prepared and characterized this year are included in Table 3 along with their physical constants and full analytical data. In essence, the appropriate amine (free base) was added to diethyl ethoxymethylenemalonate and the mixture heated to 100° to drive off the ethanol produced in the condensation.





R = CH_3, CH_3CH_2, $CH_3(CH_2)_3$, $CH_3(CH_2)_9$, CF_3CH_2,



Presumably, this reaction involves a Michael addition of the amine followed by the thermal elimination of ethanol. All of the products listed above slowly solidified after cooling to room temperature and were isolated in nearly quantitative yields. Most were quite dark in the crude state, however, all could be obtained as white solids after recrystallization. The proton spectrum for the ethoxy analog is reproduced in Figure 5, and clearly discloses the characteristic downfield shifts for the vinylic (1.66 τ, d) and amino protons (-1.14 τ, d). The proton spectra for each of the remaining analogs were quite similar as evidenced for that of the benzyloxy analog (Figure 6).

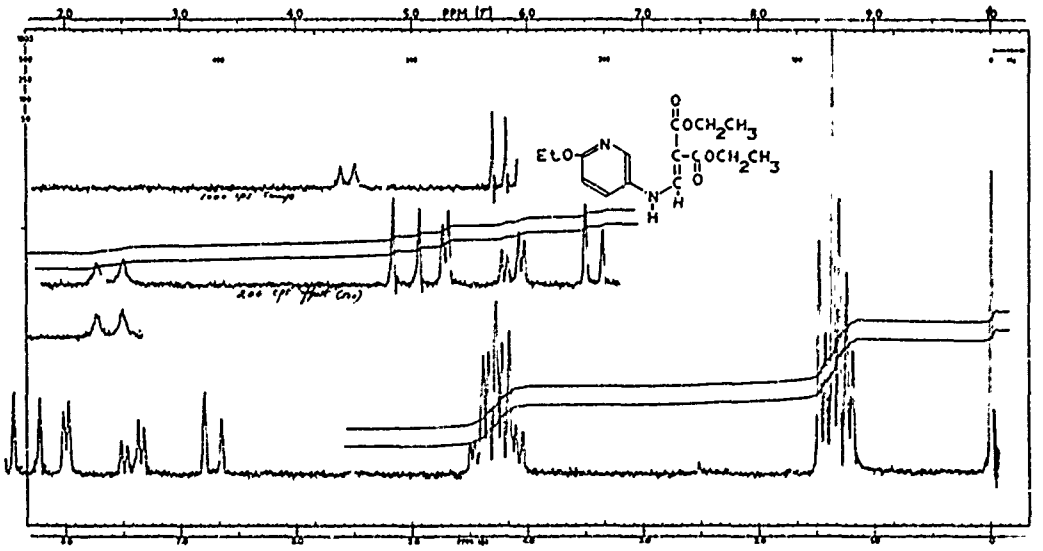


Figure 5. Proton spectrum of diethyl 6-ethoxy-3-pyridylaminomethylene-malonate ($CDCl_3$).

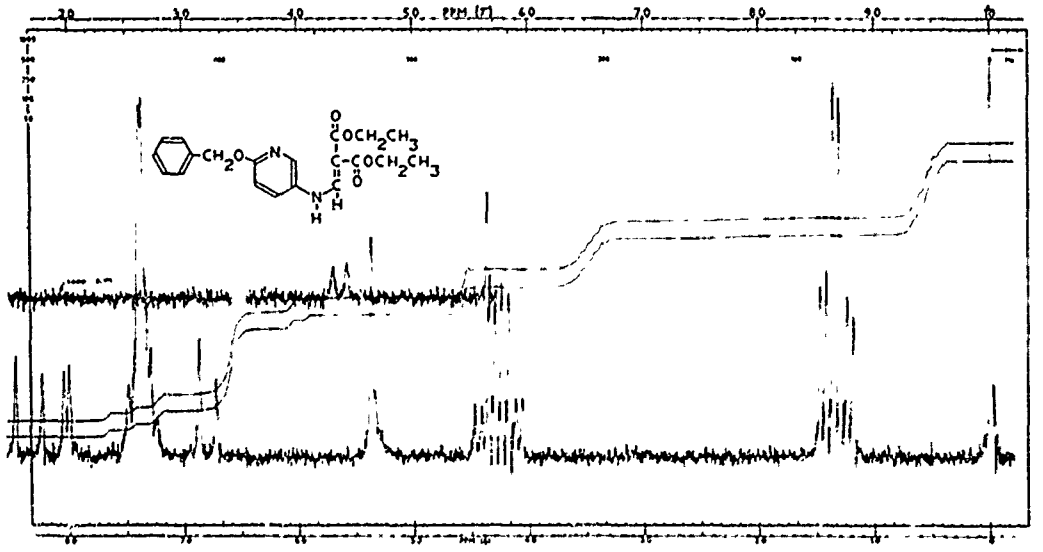


Figure 6. Proton spectrum of diethyl 6-benzyloxy-3-pyridylaminomethylene-malonate ($CDCl_3$).

The infrared spectrum for the p-chlorobenzyloxy analog (Figure 7) is also typical for all of the methylenemalonate precursors prepared this year. Both carbonyl absorptions overlap and are present near 5.8 μ. In addition, the enhanced vinylic absorption is present as a strong peak near 6.1 μ (8).

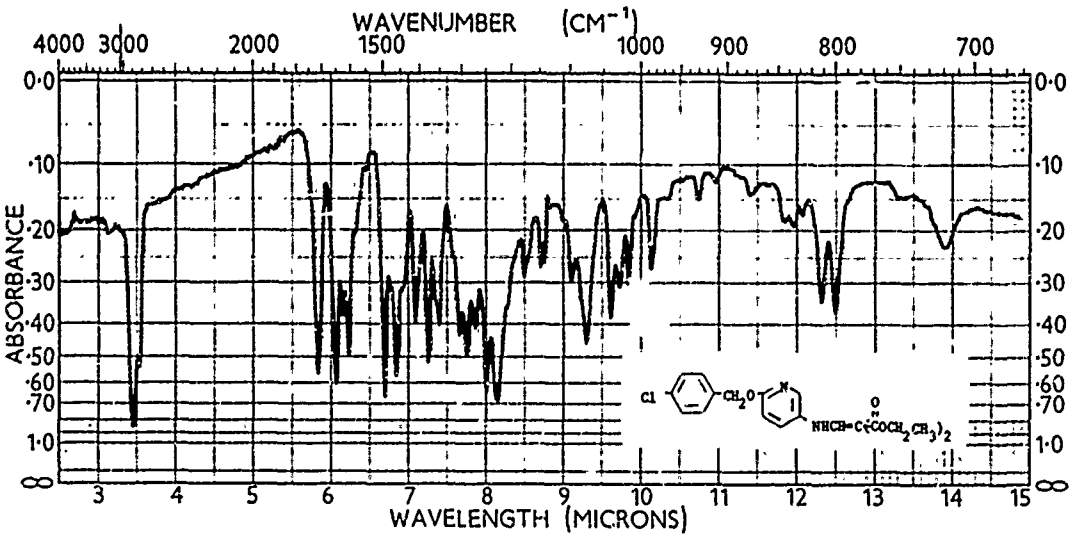


Figure 7. Infrared spectrum of diethyl 6-p-chlorobenzyloxy-3-pyridylaminomethylene malonate (nujol mull)

Table 3

6-Alkoxy-3-Pyridylaminomethylenemalonates

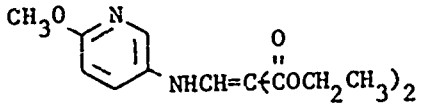
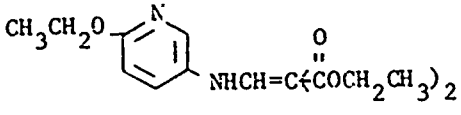
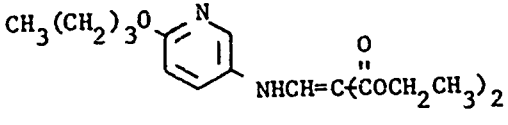
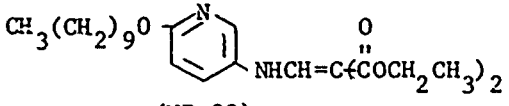
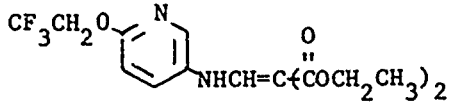
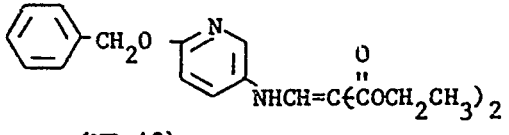
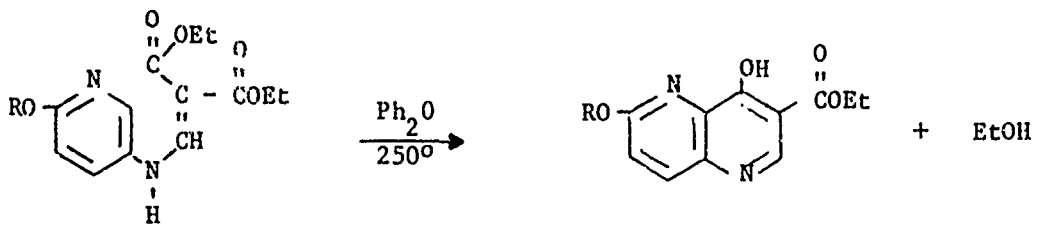
Structure	M.P., °C	Elemental Analysis C	H	N	
 (NP-10)	89-90	57.13 57.13	6.16 6.10	9.52 9.41	Theory Found
 (NP-19)	71-72	58.43 58.66	6.54 6.62	9.09 9.10	
 (NP-11)	54-55	60.70 60.54	7.19 6.98	8.33 8.25	

Table 3 (Cont'd.)

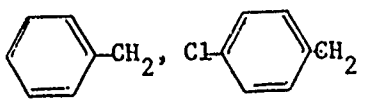
Structure	M.P., °C	Elemental Analysis		
		C	H	N
 (NP-20)	62-63	65.68 65.83	8.63 8.66	6.66 6.50
 (NP-12)	85-86	49.72 50.05	4.73 4.72	7.73 7.80
 (NP-43)	97-98	64.85 64.80	5.99 6.02	7.56 7.68
 (NP-13)	96-98	59.33 59.49	5.23 5.29	6.92 6.97

3-Carbethoxy-1,5-Naphthyridines

The title derivatives prepared and characterized this year are included in Table 4 at the end of this section. Exclusive of NI-2, each of these 1,5-naphthyridines were prepared via a thermally induced cyclization of the 3-pyridylaminomethylenemalonates in refluxing diphenyl ether solution.



R = CH_3, CH_3CH_2, $CH_3(CH_2)_3$, $CH_3(CH_2)_9$, CF_3CH_2,



In general, each of these derivatives proved to be a highly insoluble and high melting solid. The products separated from the diphenyl ether solution upon cooling, and were conveniently purified by repeated trituration with hot ethanol. The infrared spectra for the n-decyloxy and p-chlorobenzyloxy analogs are illustrative for this group and are reproduced in Figures 8 and 9 respectively. The ester carbonyl absorption is present at 5.9μ, and the heterocyclic aromatic absorptions are present as the multiple bands at 6.1-6.8μ and ca., 12-14μ. In no instance was a discrete phenolic band present near 3.0μ! Only a broad absorption from 3.1 to 3.9μ (under the nujol peak) could be ascribed to the hydrogen bonded phenolic absorption (8).

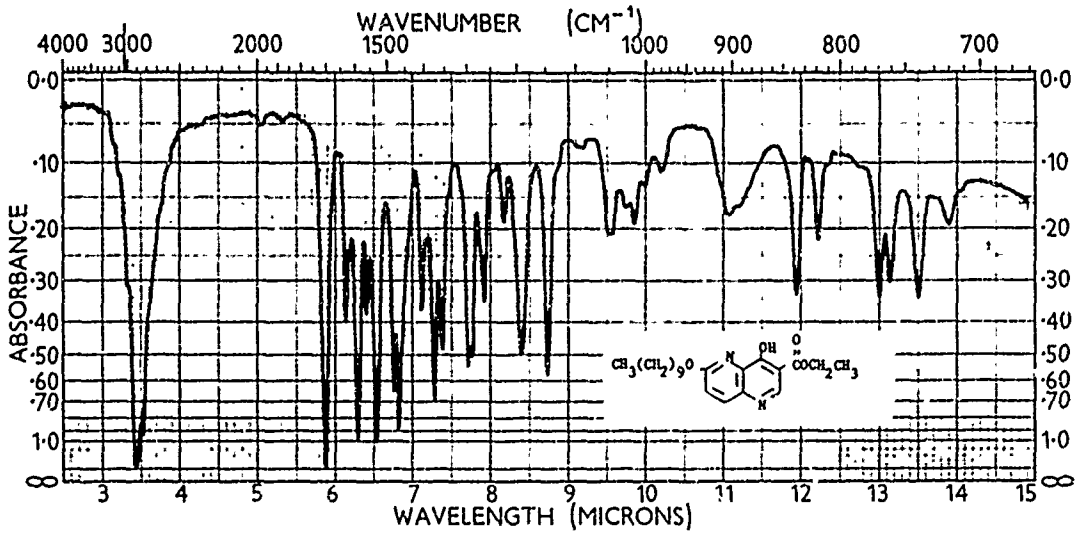


Figure 8. Infrared spectrum of 3-carbethoxy-6-n-decyloxy-4-hydroxy-1,5-naphthyridine (nujol mull)

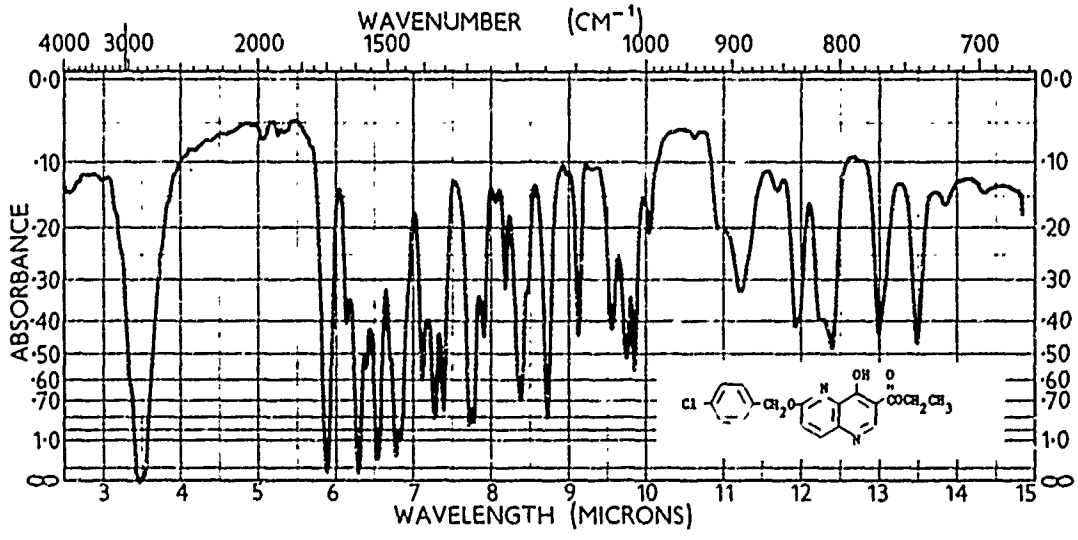
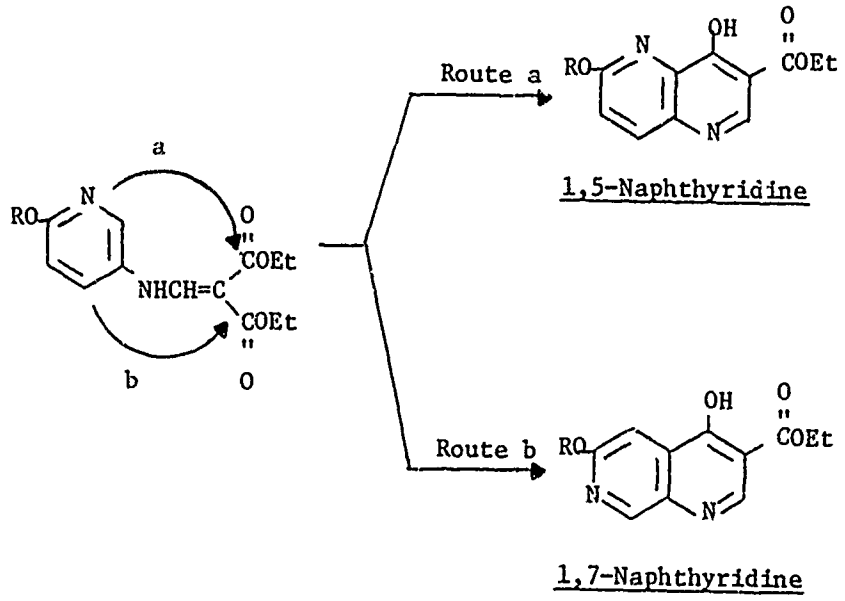


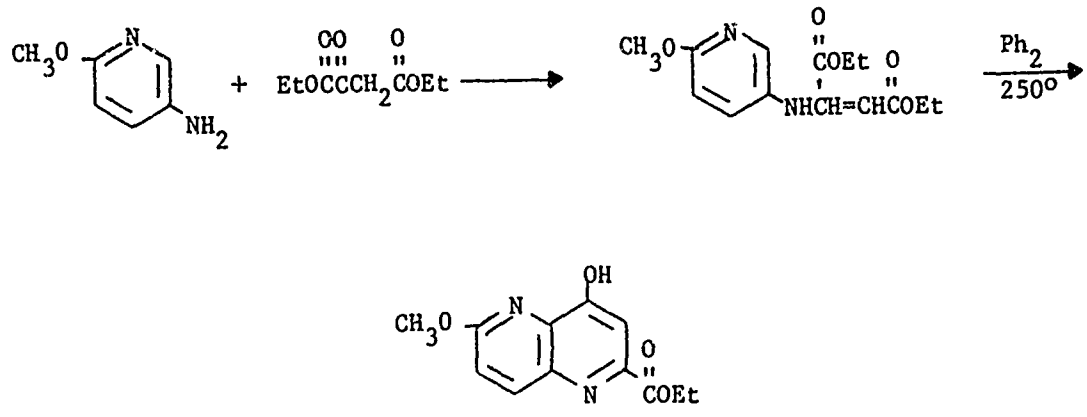
Figure 9. Infrared spectrum of 3-carbethoxy-4-hydroxy-6-(p-chlorobenzyloxy)-1,5-naphthyridine (nujol mull)

Presumably, cyclization of the methylenemalonic ester could occur at either the 2- or the 4-position of the pyridine nucleus. The resulting products could, therefore, be either a 1,5- or a 1,7-naphthyridine.



The almost total insolubility of these derivatives in any common solvent has precluded proton spectral measurements. However, as Goldberg has pointed out (5), the electron density at C-2 in 3-aminopyridine is higher than at C-1 as shown by chlorination to 2-chloro-3-aminopyridine in 90% yield (9). Moreover, the Skraup cyclization with 3-aminopyridine leads to predominant reaction at C-2 (10). Since the cyclization step is essentially an attack of the cationoid group upon the pyridine nucleus, the point of attack must be governed by the relative electron density at C-2 and C-4. These products should, therefore, be the 1,5-naphthyridines. Also, as disclosed later in this report, proton spectral measurements taken of more soluble derivatives of these esters are in complete accord with the 1,5-naphthyridine nucleus to the complete exclusion of the 1,7-isomer.

The remaining derivative in Table 4, 2-carbethoxy-4-hydroxy-6-methoxy-1,5-naphthyridine (NI-2) was prepared according to the procedure described by Goldberg (5). Condensation of 5-amino-2-methoxypyridine with ethyl ethoxyalylacetate (11) in the presence of acetic acid, and cyclization of the resulting acrylate ester afforded NI-2 in moderately high yield.



This intermediate was prepared in view of Goldberg's report that decarboxylation of the acid produced from the 3-isomer proceeded only in low yields (5). However, as we have demonstrated this year (vide infra), decarboxylation of the acid derived from NI-2 was also rewarding. The corresponding 6-methoxy-4-amino-1,5-naphthyridines were finally prepared via an alternative synthetic route (see Section 3.1.2).

Table 4

3-Carbethoxy-1,5-Naphthyridines

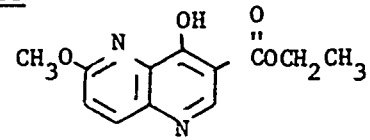
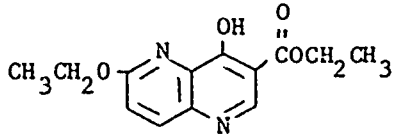
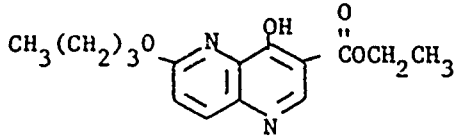
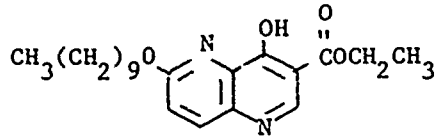
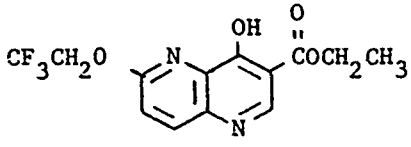
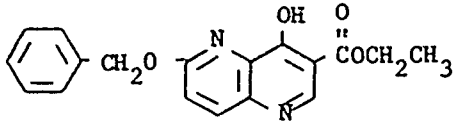
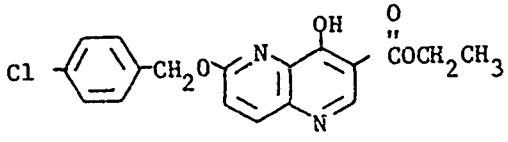
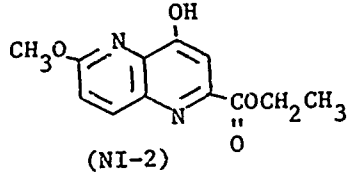
Structure	M.P., °C	Elemental Analysis C	H	N	
 (NI-1)	279-282	58.06 58.29	4.87 4.84	11.29 11.36	Theory Found
 (NI-20)	280-282 (dec.)	59.53 59.26	5.38 5.22	10.68 10.98	
 (NI-3)	277-279	62.05 62.22	6.25 6.12	9.65 9.81	
 (NI-4)	238-239	67.35 67.50	8.08 8.20	7.48 7.44	

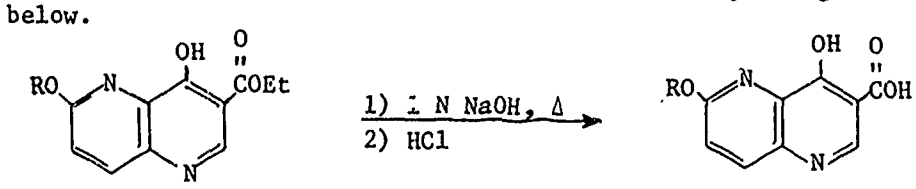
Table 4 (Cont'd.)

Structure	M.P., °C	Elemental Analysis C	H	N
 (NI-5)	303-304	49.37 49.68	3.51 3.56	8.86 8.99
 (NI-41)	275-277	66.65 66.55	4.97 4.93	8.64 8.63
 (NI-6)	285-287	60.25 60.63	4.21 4.35	7.81[a] 7.83
 (NI-2)	234-235	58.06 58.28	4.87 5.01	11.29 11.34

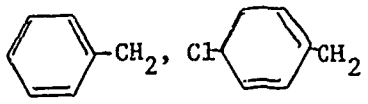
(a) Theory for Cl = 9.88; Found = 9.96

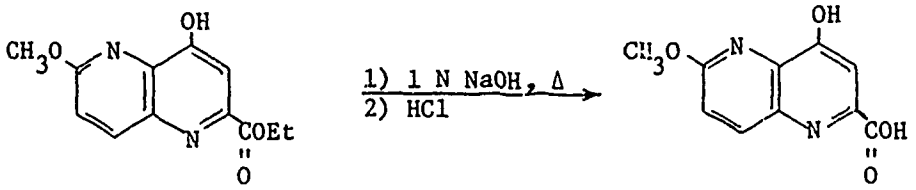
3-Carboxy-1,5-Naphthyridines

Each of the eight carbethoxy-1,5-naphthyridine esters discussed in the preceding section were converted to the corresponding acid as shown below.



R = CH_3, CH_3CH_2, $CH_3(CH_2)_3$, $CH_3(CH_2)_9$, CF_3CH_2,





In general, the 1,5-naphthyridine esters were saponified with 1N NaOH by heating to 95-100° for at least four hours. The more insoluble esters (n-decyloxy and p-chlorobenzyloxy) required heating for at least one day before complete reaction occurred. After cooling, the solutions were acidified to congo red at which point a thick, pasty suspension of the free acid was produced. These acids tenatiously held water and proved to be very difficult to dry completely. Prolonged heating under reduced pressure did, however, afford tractable solids. The five acids which have been characterized this year are included in Table 5 at the end of this section. The remaining three acids have also been prepared in scale and are currently being purified before proceeding with the remaining steps in this synthesis. Both the ethoxy and trifluoroethoxy analogs consistently analyzed as hydrates even when subjected to drying under vacuum at 110°. The infrared spectrum for the trifluoroethoxy acid (Figure 10) is to be contrasted with the n-butoxy acid (Figure 11). The water of hydration in the trifluoroethoxy derivative may be ascribed to the sharp peak near 2.9 μ in Figure 10.

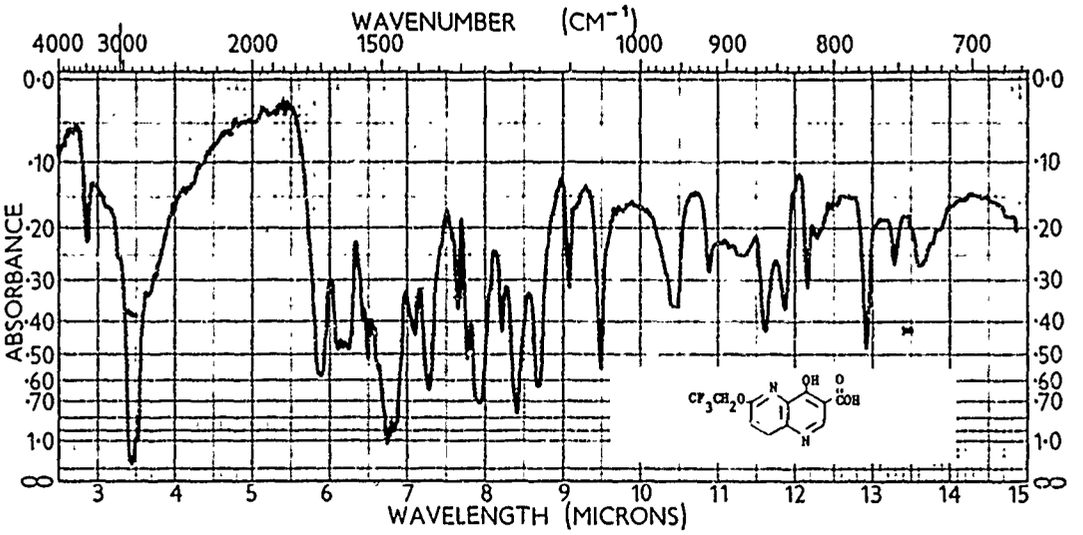


Figure 10. Infrared spectrum of 3-carboxy-4-hydroxy-6-(2,2,2-trifluoroethoxy)-1,5-naphthyridine mono-hydrate (nujol mull)

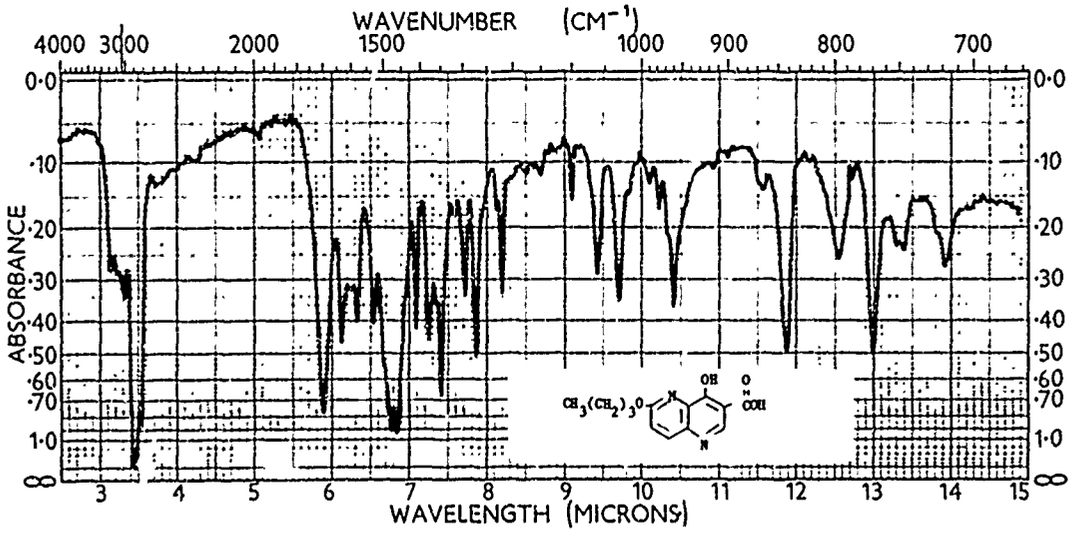


Figure 11. Infrared spectrum of 6-n-butoxy-3-carboxy-4-hydroxy-1,5-naphthyridine (nujol mull)

Table 5

3-Carboxy-1,5-Naphthyridines

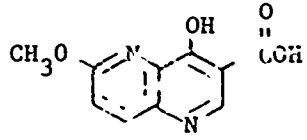
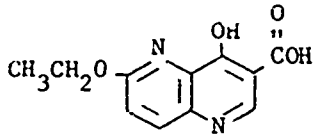
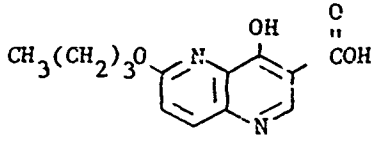
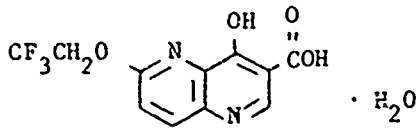
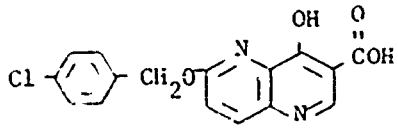
Structure		M.P., °C	Elemental Analysis C	H	N	
 (NI-7)		>310	54.55 54.31	3.66 3.61	12.73 12.63	Theory Found
 (NI-21)	1/2 H_2O	273-275	54.32 54.38	4.56 4.38	11.52 11.95	
 (NI-8)		254-255	59.53 58.98	5.38 5.38	10.68 10.52	

Table 5 (Cont'd.)

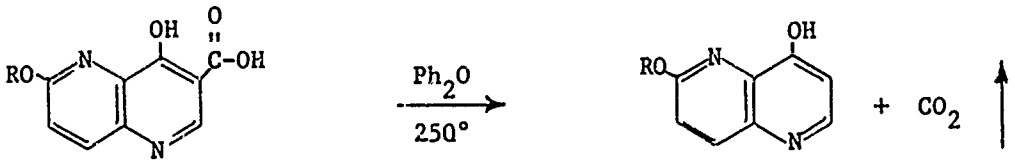
Structure	M.P., °C	Elemental Analysis		
		C	H	N
 (NI-9)	280-281	43.15 43.05	2.96 2.83	9.15 9.00(a)
 (NI-22)	285-287	58.10 57.97	3.35 3.46	3.47(b) 8.53

(a) A second sample was recrystallized twice from ethanol and dried at 100° (0.10 mm). Found: C, 43.24; H, 2.52; N, 9.11.

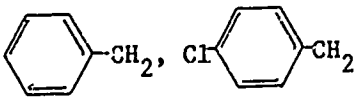
(b) Theory for Cl = 10.72; Found = 10.50.

4-Hydroxy- and 4-Chloro-1,5-Naphthyridines

The next step involved in the synthetic route as shown in Scheme 1 involved the thermal decarboxylation of the acids discussed in the preceding section. This decarboxylation was effected in refluxing diphenyl ether solution.



R = CH_3, CH_3CH_2, $CH_3(CH_2)_3$, $CH_3(CH_2)_9$, CF_3CH_2,



Each of the acids were added to the refluxing phenyl ether solution as quickly as possible, and the evolution of carbon dioxide was readily apparent (effervescence). After the addition was completed, the solutions were heated for only five to ten additional minutes before quickly cooling to room temperature. The crude products separated from solution and were isolated by adding heptane and filtering. The hydroxy analogs which have been characterized to date are included in Table 6 at the end of this section. The infrared spectra for both the pure 6-n-butoxy- and 6-(2,2,2-trifluoroethoxy)-4-hydroxy-1,5-naphthyridines (recrystallized from ethanol) are reproduced in Figures 12 and 13, respectively.

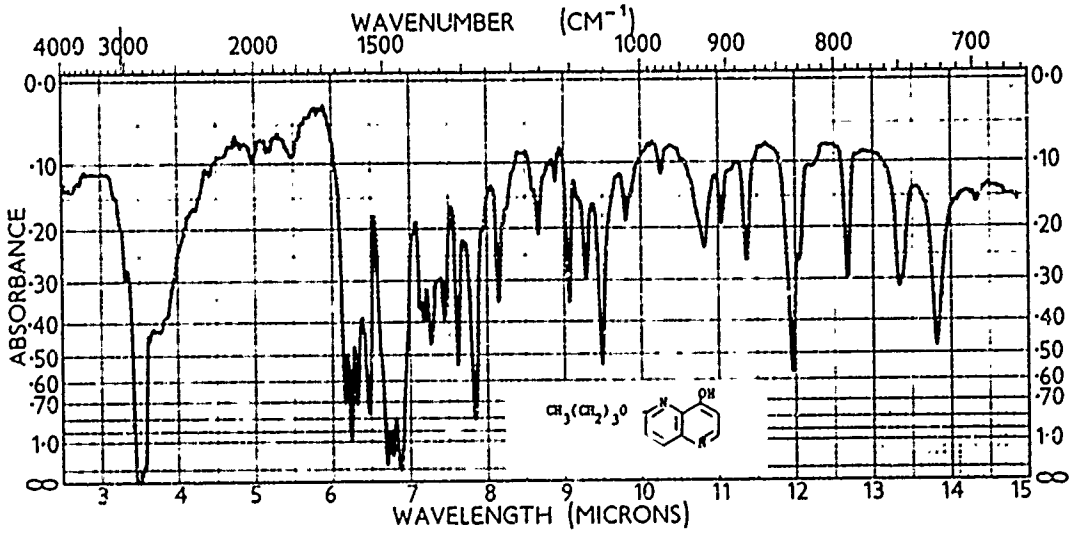


Figure 12. Infrared spectrum of 6-n-butoxy-4-hydroxy-1,5-naphthyridine (nujol mull)

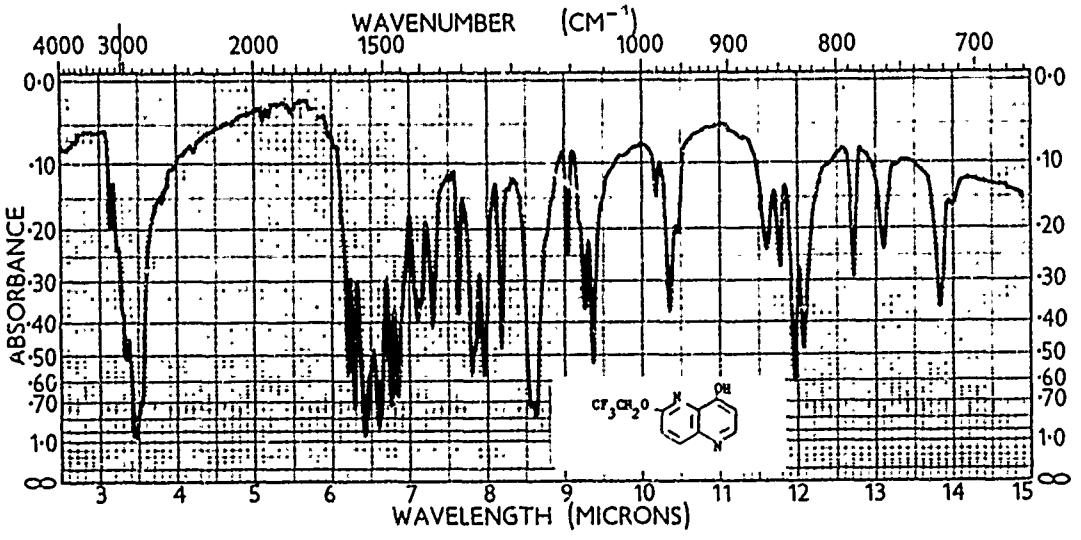
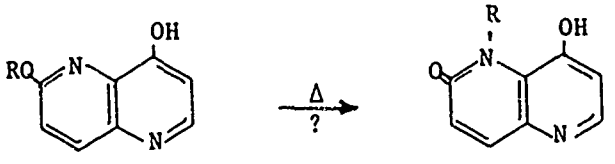
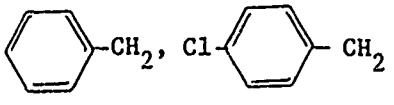


Figure 13. Infrared spectrum of 4-hydroxy-6-(2,2,2-trifluoroethoxy)-1,5-naphthyridine (nujol mull)

It is to be emphasized that the infrared spectra for both of these derivatives (when pure) exhibited no carbonyl absorptions near 6.0 μ. This is to be contrasted with the spectra of the crude 4-hydroxy derivatives derived from the remaining naphthyridine acids listed above. In all cases, a prominent band near 6.0 μ was present which strongly suggests that translocation of the 6-alkoxy group from the ether linkage to the ring-5 nitrogen atom had occurred concurrently with the decarboxylation.

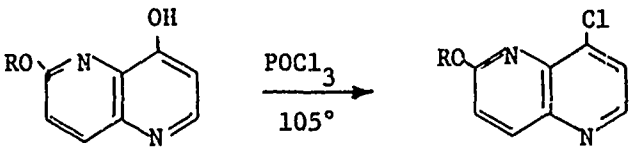


R = CH_3CH_2, $CH_3(CH_2)_9$, 

While we have not as yet been able to isolate pure samples of these transformation products, the succeeding step of Scheme 1 as applied to the crude materials has afforded derivatives which lend credence to this supposition (vide infra). Also, decarboxylation of 3-carboxy-4-hydroxy-6-methoxy-1,5-naphthyridine (NI-7) could not be effected. Moderately, violent erruptions were noted with the portionwise addition of this acid to the hot

diphenyl ether. As fully discussed in Section 3.1.2, however, our use of an alternative synthetic procedure has allowed us to circumvent these difficulties.

The conversions of the purified 6-alkoxy-4-hydroxy-1,5-naphthyridines to the corresponding 4-chloro analogs were conveniently effected in refluxing phosphorus oxychloride solution. The reactions which have afforded characterizable derivatives are illustrated below.



R = $CH_3(CH_2)_3$, CF_3CH_2

Both products were isolated in moderately high yields, and the analytically pure examples (Table 6) were obtained by recrystallization from pentane at -70°. The infrared spectra typically displayed few characteristic bands other than the aromatic absorptions. The proton spectra, however, were consistent solely with the 1,5-naphthyridine ring nucleus as formulated (Figures 14 and 15). The two A_2B_2 doublets in the aromatic region clearly differentiate these products from any 1,7-naphthyridine which conceivably could have been formed in the thermal cyclization of the 3-pyridylaminomethylenemalonates.

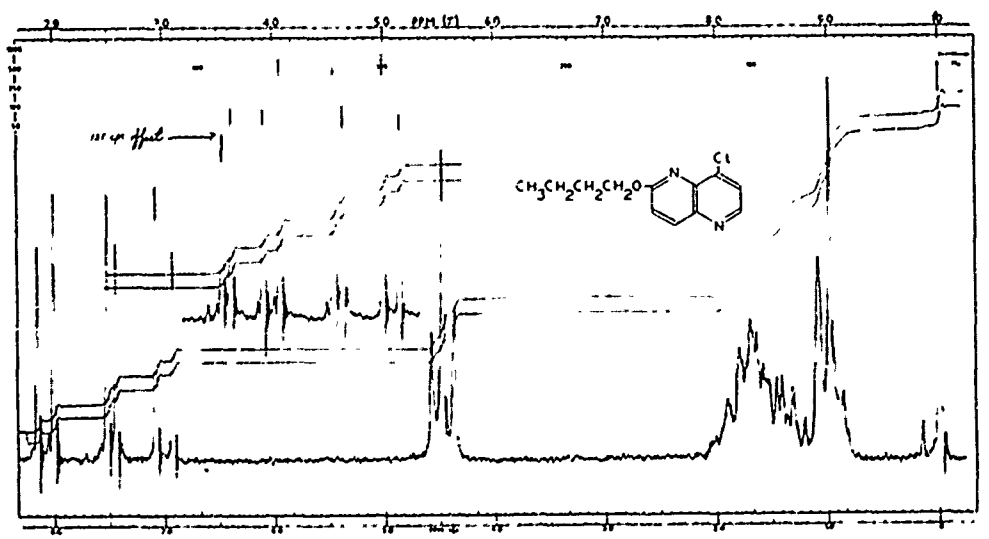


Figure 14. Proton spectrum of 6-n-butoxy-4-chloro-1,5-naphthyridine (CCl_4)

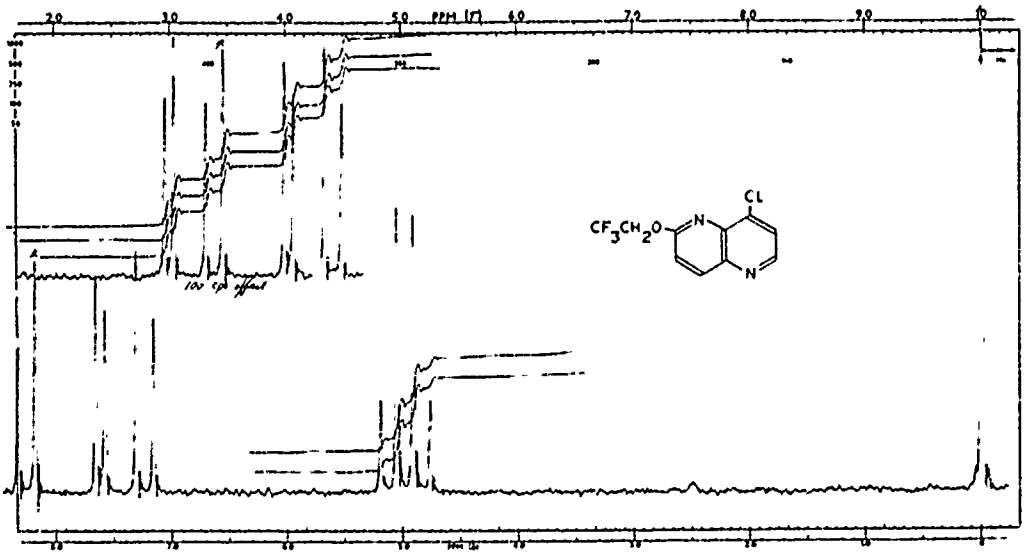
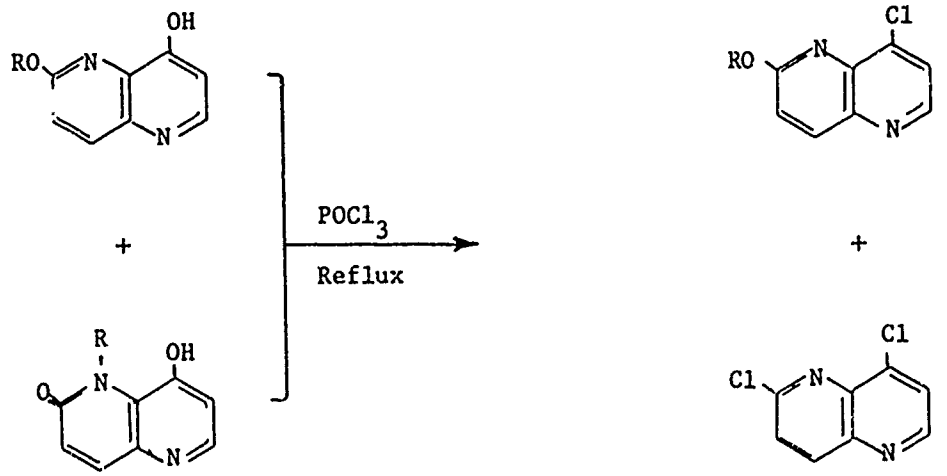
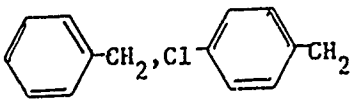


Figure 15. Proton spectrum of 4-chloro-6-(2,2,2-trifluoroethoxy)-1,5-naphthyridine ($CDCl_3$).

As mentioned earlier in this section, the crude 4-hydroxy analogs which exhibited an absorption near 6.0 μ were assumed to be mixtures. This has been experimentally verified in the chlorination reactions performed upon them to date.

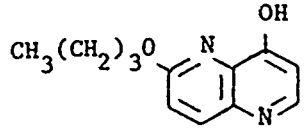
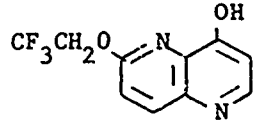
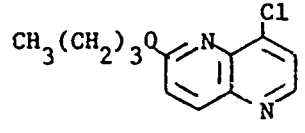
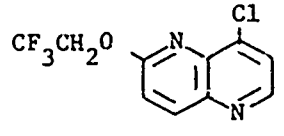


R = CH_3CH_2, 

With the crude 6-ethoxy-4-hydroxy analog, a 50:50 mixture of the 4,6-dichloro-1,5-naphthyridine and the 6-ethoxy-4-chloro-1,5-naphthyridine was produced (see Experimental). With the benzyloxy analogs, only the 4,6-dichloro-1,5-naphthyridine was observed. As illustrated by the equation above, a plausible source of the 4,6-dichloro-1,5-naphthyridine is the N-alkyl-naphthyridone structure by analogy to similar reactions in the quinoline series (12). The proof of structure for the 4,6-dichloro-1,5-naphthyridine rests upon its physical and spectral properties as well as its formation via an unambiguous synthetic route (see Section 3.1.2).

Table 6

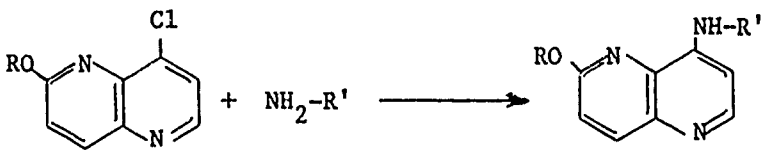
4-Hydroxy- and 4-Chloro-1,5-Naphthyridines

Structure	M.P., °C	Elemental Analysis C	H	N	
 (NI-10)	183-184	66.03 65.74	6.47 6.39	12.84 12.92	Theory Found
 (NI-11)	293-294	49.19 49.57	2.89 2.95	11.48 11.32	
 (NI-12)	33-34	60.89 60.63	5.53 5.49	11.84 11.91	
 (NI-13)	83-84	45.73 45.91	2.30 2.41	10.67 (a) 10.67	

(a) Theory for Cl = 13.50; Found = 13.15

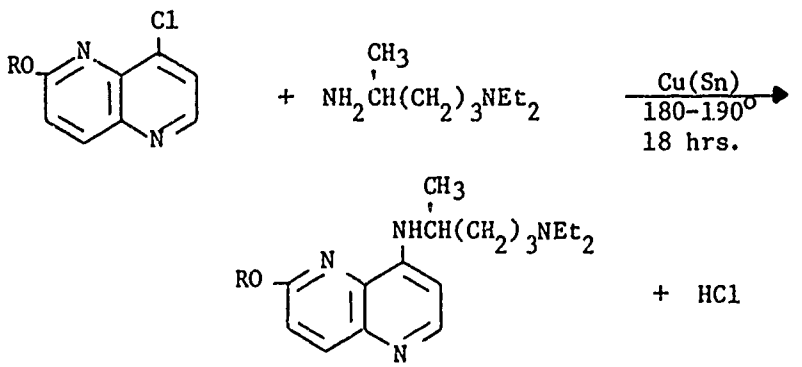
6-Alkoxy-4-Amino-1,5-Naphthyridines

As disclosed earlier in Scheme 1, the final step in the classical EMME synthesis involves displacement at the 4-position in the 4-chloro-6-alkoxy-1,5-naphthyridine intermediates by the primary amino group of selected diamines.



This year, we have prepared several target structures which contain both the pamaquine and pentaquine side chains. A summary of the physical constants and analytical data for the target compounds prepared via their route are included in Table 7 at the end of this section; a discussion of their preparative chemistry is included below. Also, near the beginning of our research, Walter Reed personnel expressed interest in securing analogs which incorporate the primaquine side chain (containing a primary terminal amine function). A discussion of our primary synthetic approach to these derivatives is also included below.

The inclusion of the pamaquine side chain onto the 6-n-butoxy- and 6-(2,2,2-trifluoroethoxy)-4-chloro-1,5-naphthyridines was effected essentially as Goldberg has described for the butoxy analog (5). The appropriate 4-chloro derivative was added to an excess of novaldiamine and a catalytic quantity of copper-bronze at room temperature. The substitution reaction was then effected by heating to 180-190° for eighteen hours.



R = $CH_3(CH_2)_3$, CF_3CH_2

The hydrochloric acid generated in the reaction was neutralized by the addition of an excess of aqueous base, and the product and excess amine were then extracted into ether. After drying and removal of the ether, the residual brown liquids were subjected to molecular distillations. The excess novaldiamine was first distilled off at a bath temperature of ca., 70-110° (0.10 mm). The desired target compounds were subsequently distilled at the bath temperature and pressure listed in Table 7. Both products were obtained analytically pure as orangish-yellow oils in high yield (70-90%). The infrared and proton spectra for the 6-(2,2,2-trifluoroethoxy)-4-(4-diethylamino-1-methylbutylamino)-1,5-naphthyridine analog are reproduced in Figures 16 and 17, respectively.

The infrared spectrum (Figure 16) clearly discloses the presence of the aromatic amino group at 3.1μ. In addition, the following assignments have been made for the proton spectrum (Figure 17): 1.57τ (1H, d, ring H-); 1.88τ (1H, d, ring H-8); 2.95τ (1H, d, ring H-7); 3.49τ (1H, d, ring H-3); 4.02τ (1H, d, N-H), $J_{N-H,\ C-H}$ = 8.1 Hz; 5.15τ (2H, q, CH_2O), J_{HF} = 8.4 Hz; 6.30τ (1H, broad m, C-H); 7.51τ (6H, q, N-CH_2-) 8.2-9.2τ (13H, m, side chain -CH_2-, -CH_3); $J_{2,3}$ = 5.1 Hz; and $J_{7,8}$ = 9.0 Hz.

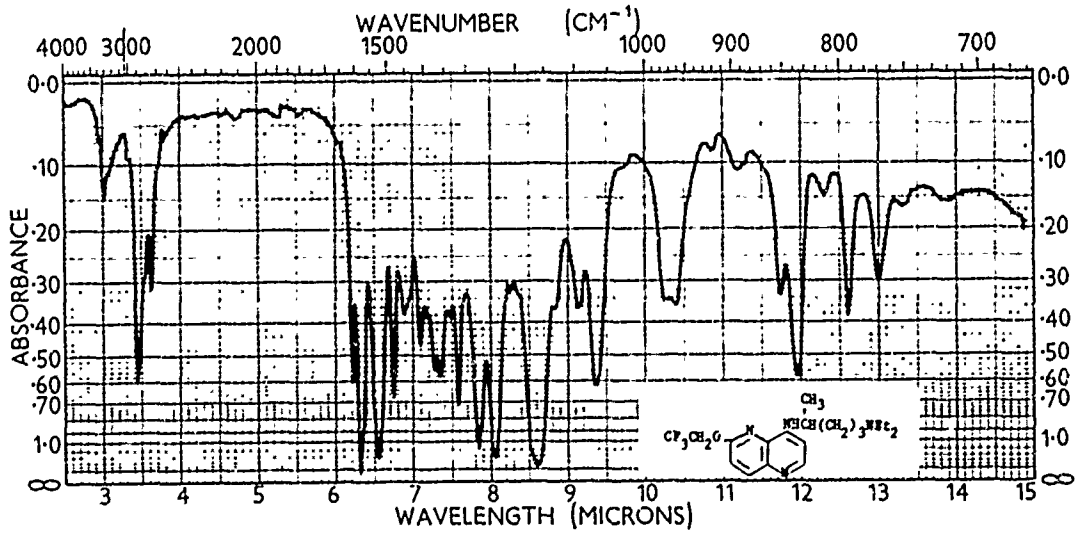


Figure 16. Infrared spectrum of 6-(2,2,2-trifluoroethoxy)-4-(4-diethylamino-1-methylbutylamino)-1,5-naphthyridine (liquid film)

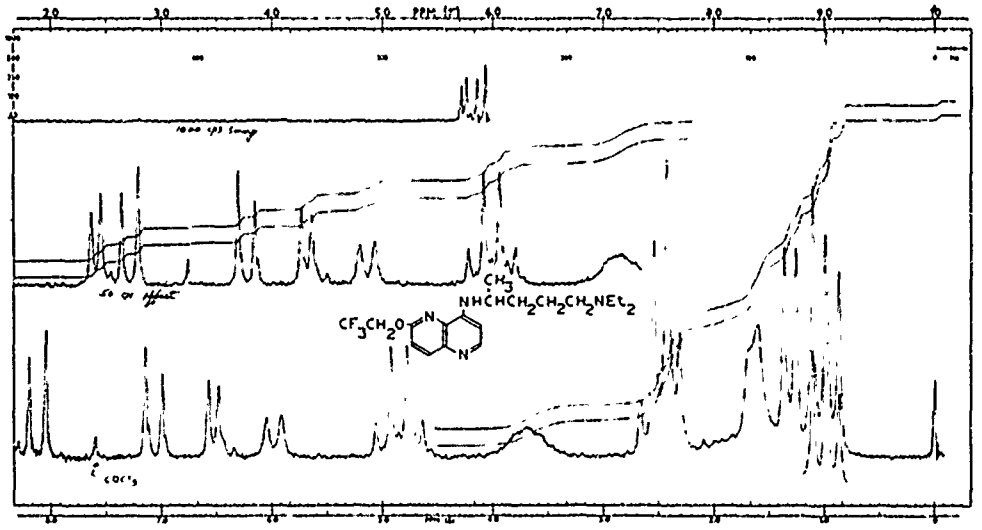
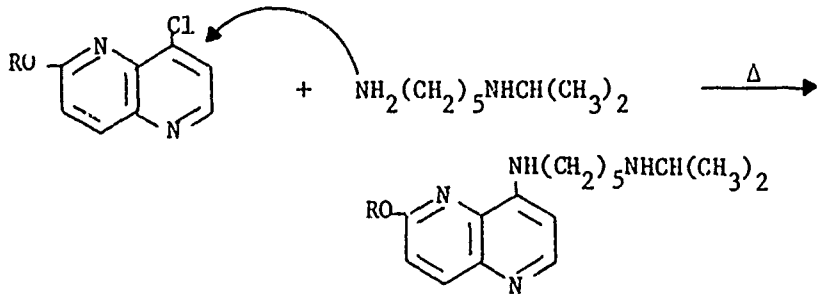


Figure 17. Proton spectrum of 6-(2,2,2-trifluoroethoxy)-4-(4-diethylamino-1-methylbutylamino)-1,5-naphthyridine ($CDCl_3$)

The inclusion of the pentaquine side chain onto the 6-alkoxy-4-amino-1,5-naphthyridines has also been effected this year. Our initial synthetic route to these derivatives involved the selective displacement of the primary amino group of 5-isopropylaminopentylamine (13) on the chlorine atom present in the 4-chloro-6-alkoxy-1,5-naphthyridines.



R = $CH_3(CH_2)_3$, CF_3CH_2

The reaction conditions and work-up were essentially the same as that discussed for the pamaquine side chain analogs. Both products were isolated as orange-amber oils of analytical purity (Table 7) in low to moderate yield by molecular distillation. The infrared spectrum of the 6-butoxy analog is reproduced in Figure 18 and again discloses the presence of the N-H stretching frequencies near 3.0 μ. The proton spectra for both the 6-butoxy- and 6-(2,2,2-trifluoroethoxy)- analogs are reproduced in Figures 19 and 20, respectively. Of particular importance is the fact that the N-H resonance is present as the predicted broad triplet near 3.8 τ. Also, the presence of only one isopropyl doublet near 9.0 τ conclusively proves that the point of attachment of the pentaquine side chain is solely at the primary amino group. Presumably, the greater steric requirements necessary for reaction at the secondary amino group of their diamine leads to exclusive attack by the primary amine function. This is in agreement with Tarbell's supposition (not conclusively proven) that only the primary amino group of 3-isopropylaminopropylamine reacted at the 4-position present in 4,7-dichloroquinoline (14).

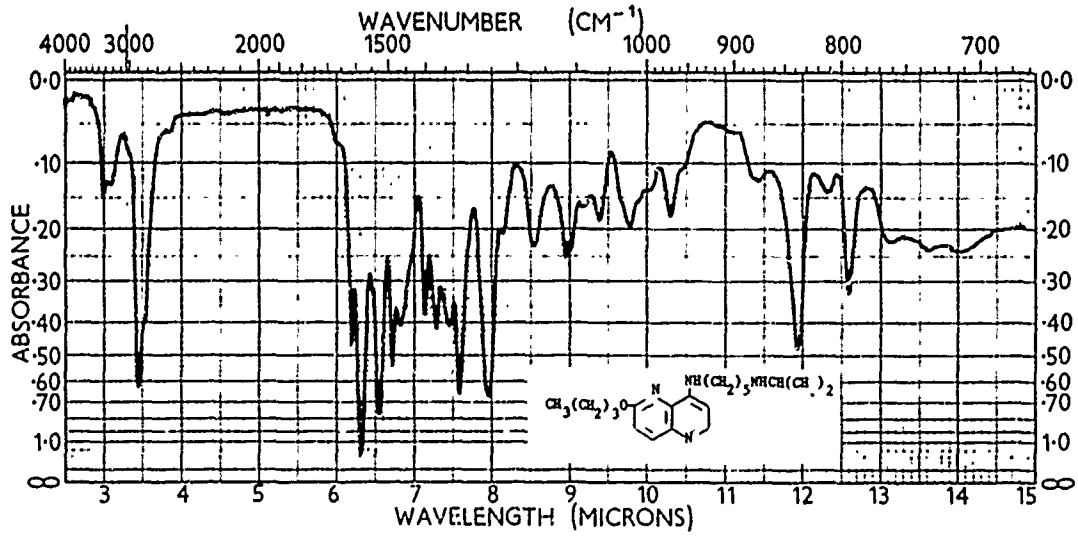


Figure 18. Infrared spectrum of 6-n-butoxy-4-(5-isopropylaminopentylamino)-1,5-naphthyridine (liquid film)

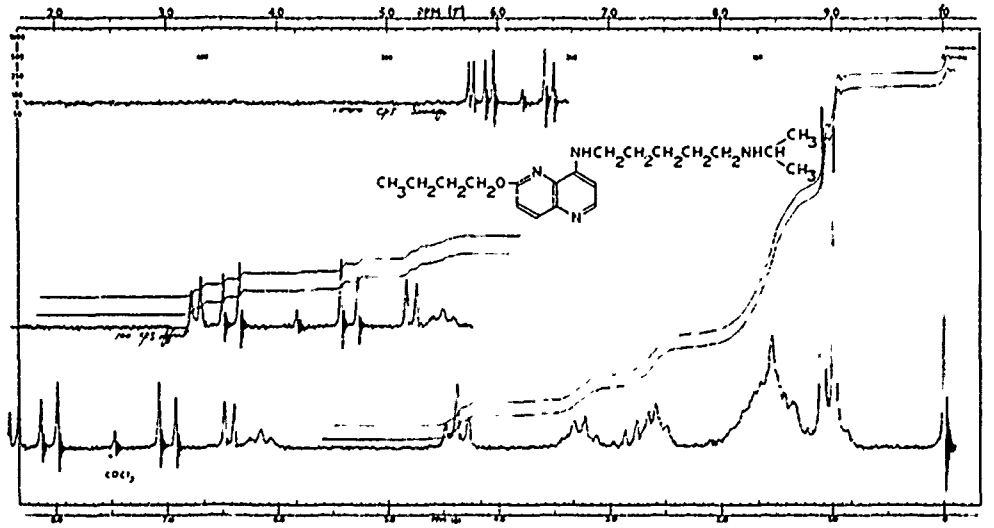


Figure 19. Proton spectrum of 6-n-butoxy-4-(5-isopropylaminopentylamino)-1,5-naphthyridine ($CDCl_3$)

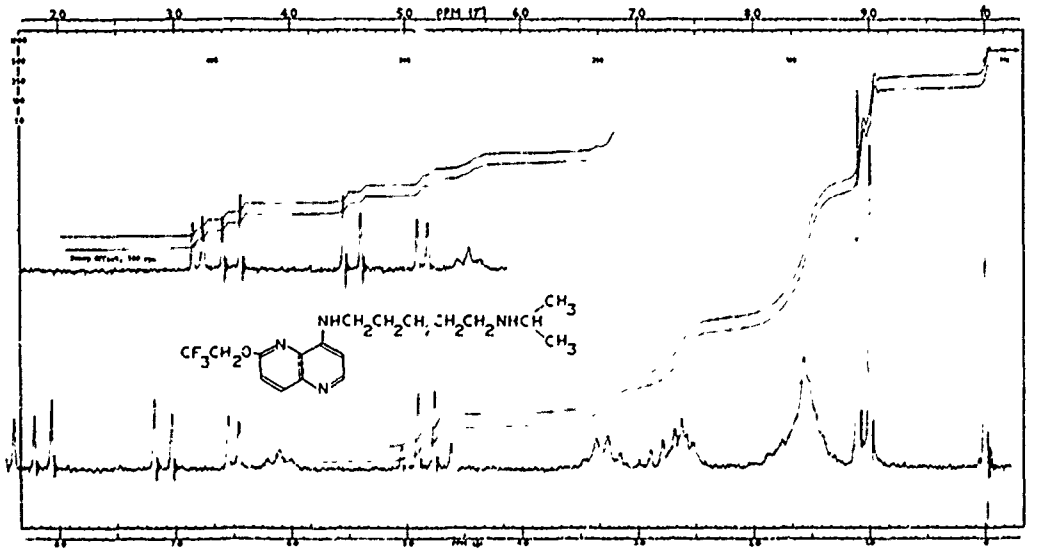
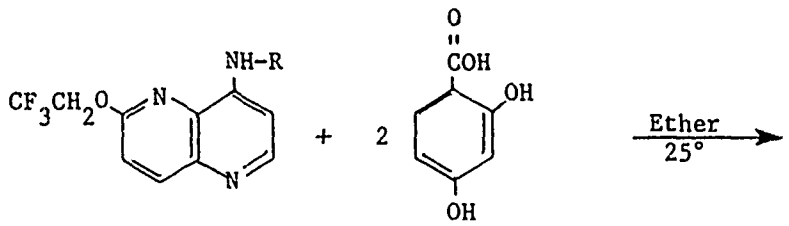
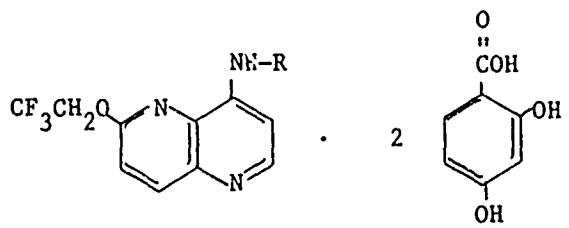


Figure 20. Proton spectrum of 6-(2,2,2-trifluoroethoxy)-4-(5-isopropylaminopentylamino)-1,5-naphthyridine ($CDCl_3$).

Our initial attempts to prepare stable, crystalline salts of these 6-alkoxy-4-amino-1,5-naphthyridine derivatives were fought with difficulties. No crystalline hydrochlorides, sulfates or phosphates could be isolated. In one run, a crystalline citrate of the 6-butoxy analog was observed. However, upon workup, this salt proved to be very hygroscopic and quickly turned into a waxy solid. This is in agreement with Adam's report that a structurally similar 4-amino-1,5-naphthyridine would not form an isolable hydrochloride, hydroiodide, phosphate or citrate (4). Two of the products did, however, form stable crystalline dipicrates. The physical constants and analytical data for these salts are included in Table 7. It is to be emphasized that the dipicrates included in Table 7 were utilized for characterization purposes only. We did not send them for biologic testing in view of the well-known toxicity of picrate salts. In our later research, we had much greater success in preparing well characterizable β-resorcylates which contain a biologically acceptable gegen-ion (15). Accordingly, the β-resorcylate salts of both trifluoroethoxy analogs were prepared by the slow addition of an ether solution of β-resorcylic acid to the free bases in ether solution at room temperature.





R = $-CH(CH_2)_3NEt_2$, $(CH_2)_5NHCH(CH_3)_2$

The precipitated salts were then isolated by filtration. It should be noted that the filtrations had to be conducted under a nitrogen atmosphere since the salts were mildly hygroscopic during workup. After washing several times with ether and then drying under reduced pressure, however, both products were isolated as white solids which did not exhibit any deliquescent properties. Full analytical data are included in Table 7, and the infrared spectrum for the 6-(2,2,2-trifluoroethoxy)-4-(5-isopropylaminopentylamino)-1,5-naphthyridine di-β-resorcylate is reproduced in Figure 21.

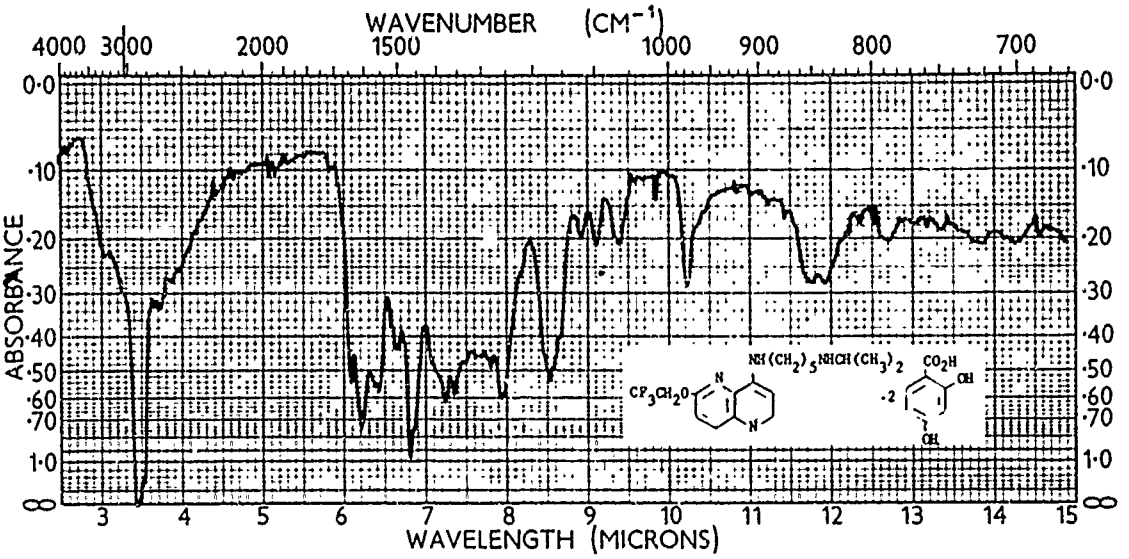
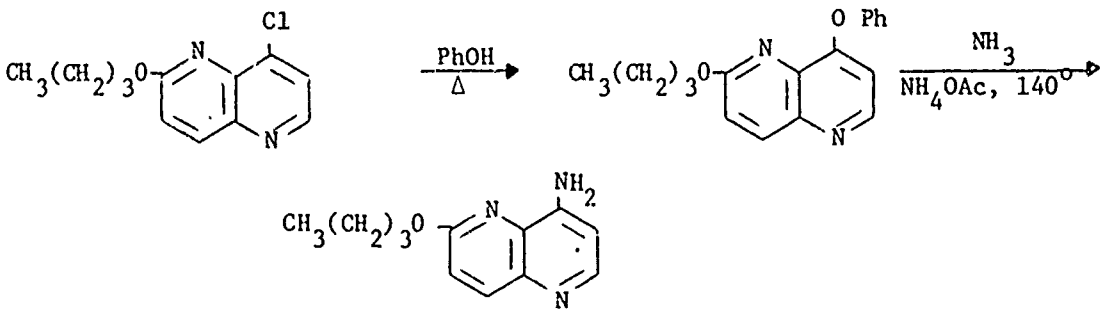


Figure 21. Infrared spectrum of 6-(2,2,2-trifluoroethoxy)-4-(5-isopropylaminopentylamino)-1,5-naphthyridine, di-β-resorcylate (nujol mull).

The last two intermediates listed in Table 7 were prepared in conjunction with our studies directed at the inclusion of the primaquine chain chain onto these 6-alkoxy-4-amino-1,5-naphthyridines. The preparation of 4-amino-6-n-butoxy-1,5-naphthyridine (NI-24) could be effected only through the intermediary of the 4-phenoxy analog.



In our hands, the pure 4-amino-6-n-butoxy-1,5-naphthyridine (heptane-charcoal) melted about ten degrees higher than reported in the literature (5). The proton spectrum for this intermediate is reproduced in Figure 22. The two 4-amino protons are present as the broad resonance near 4.55 τ.

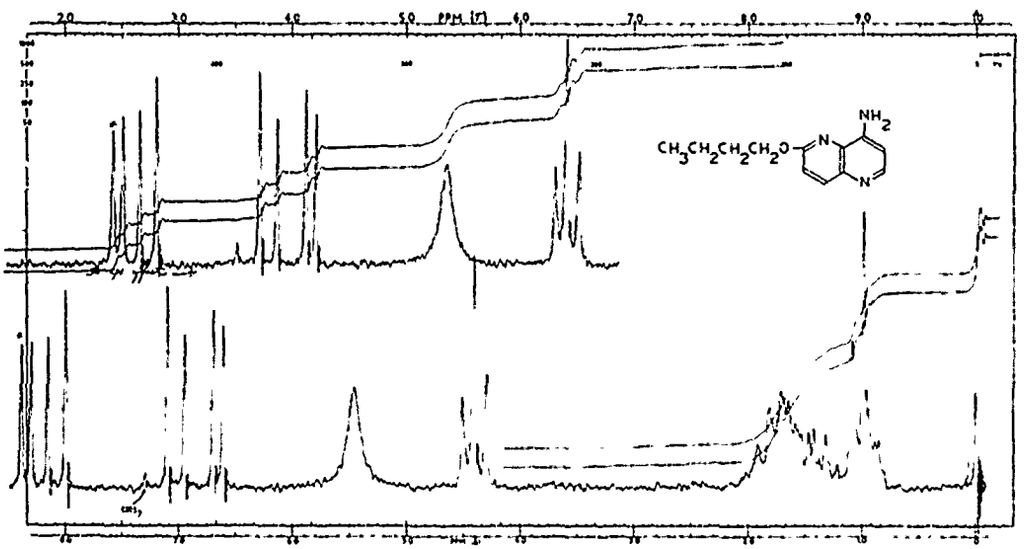
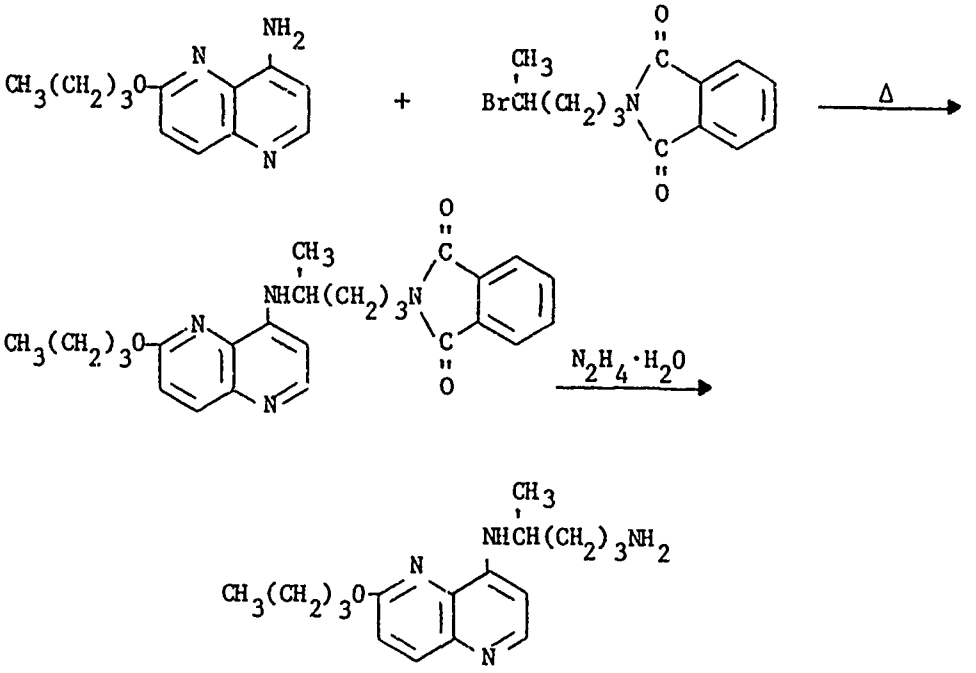


Figure 22. Proton spectrum of 4-amino-6-n-butoxy-1,5-naphthyridine ($CDCl_3$).

In a preliminary attempt to introduce the primaquine side chain onto NI-24, we reacted this amine with one-half mole-equivalent of 2-bromo-5-phthalimidopentane (16) in accord with the usual technique.



After the standard work-up (see Experimental), the sole isolable product proved to be the hydrochloride salt (NI-35) of the 4-amino-6-n-butoxy-1,5-naphthyridine starting material (NI-24). Since this procedure for the introduction of the primaquine side chain onto the 4-amino-1,5-naphthyridines has proven unrewarding, we are presently employing alternative procedures as reported in the literature (17).

Table 7

4-Amino-1,5-Naphthyridines

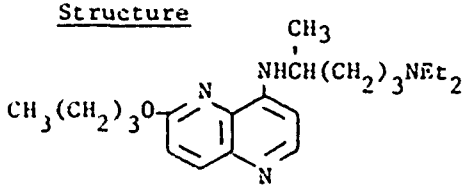
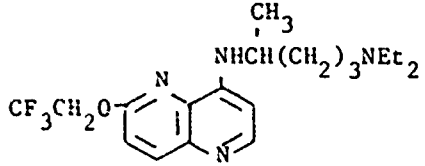
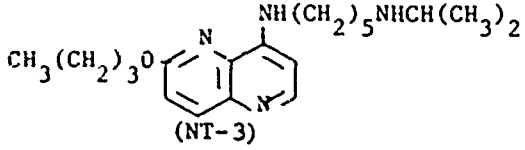
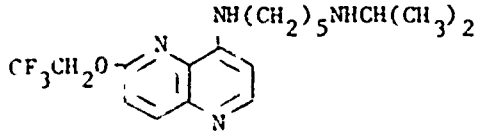
Structure	M.P., °C B.P., °C(mm)	Elemental Analysis C	 H	 N	
 (NT-1)	160-170(0.10) (a)	70.35 70.41	9.56 9.62	15.63 15.56	Theory Found
 (NT-2)	130-140(0.06) (a)	59.36 59.09	7.08 7.25	14.57 (b) 14.34	
 (NT-3)	150-170(0.10) (a)	69.73 69.34	9.36 9.55	16.26 16.16	
 (NT-8)	150-158 (0.08) (a)	58.36 58.40	6.80 7.02	15.13 15.00	

Table 7 (Cont'd.)

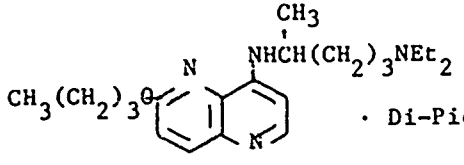
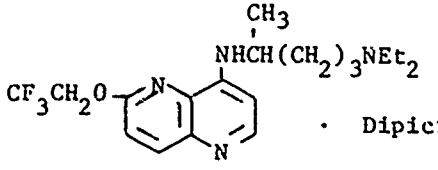
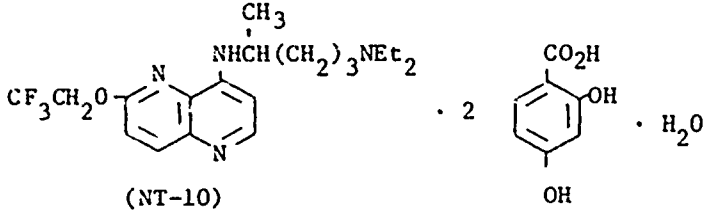
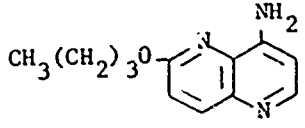
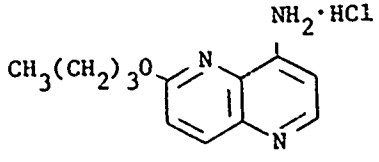
Structure	M.P., °C B.P., °C(mm)	Elemental Analysis C	 H	 N
 · Di-Picrate (c)	171-172	48.53 48.35	4.94 5.04	17.15 17.24
 · Dipicrate (c)	192-194	44.18 44.36	3.95 3.7c	16.61 16.47
 (NT-10)	105-106	55.77 55.65	5.82 5.60	7.88 (d) 7.84
 (NT-9)	106-109	56.63 57.02	5.50 5.67	8.26 (e) 8.95

Table 7 (Cont'd.)

Structure	M.P., °C B.P., °C(mm)	Elemental Analysis C	 H	 N
 (NI-24)	102-103	66.34 66.72	5.96 6.94	19.34 19.09
 (NI-35)	212-215	56.80 56.82	6.36 6.27	16.56 16.47

(a) Molecular distillation.

(b) Theory for F = 14.83; Found = 14.62.

(c) These compounds were prepared for characterization purposes only; they were not submitted for biologic testing.

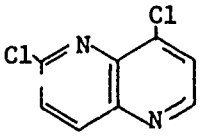
(d) Theory for F = 8.02; Found = 8.21.

(e) Theory for F = 8.40; Found = 8.75.

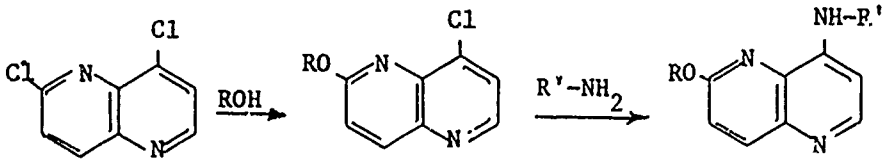
3.1.2 Modified EMME Procedure

As explained in detail in the preceding section, our use of the conventional EMME (ethoxymethylenemalonic ester) procedure by analogy to Goldberg's work (5) did not prove to be generally applicable. The major complicating factor was the failure to induce thermal decarboxylation in several of the intermediate 1,5-naphthyridine carboxylic acids. While target derivatives could be obtained via the conventional EMME procedure, the more biologically interesting analogs (6-alkoxy substituent = methoxy, ethoxy, benzyloxy) were unattainable. In this section, we have reported our use of an alternative synthetic route for the introduction of alkoxy functionality into the 6-position of the 4-amino-1,5-naphthyridines. The use of this alternative synthetic procedure has already provided derivatives of the 6-alkoxy-4-amino-1,5-naphthyridines which could not be obtained via the classical technique.

The essential feature of this alternative synthetic procedure involves the synthesis of 4,6-dichloro-1,5-naphthyridine,



as a key intermediate. Selective reaction at the 6-position of 4,6-dichloro-1,5-naphthyridine, followed by displacement of the 4-chlorine by diamines provides a viable route to the target 6-alkoxy-4-amino-1,5-naphthyridines.



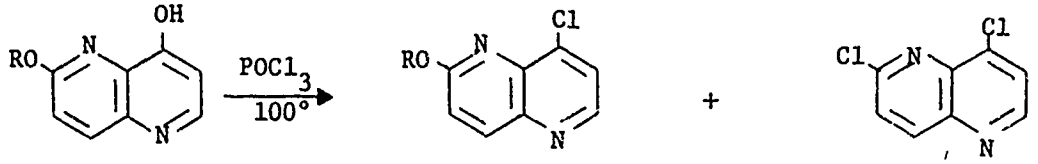
R = CH_3, CH_3CH_2

R' = $-CH(CH_2)_3NEt_2$, $-(CH_2)_5NHCH(CH_3)_2$

In the subsections below, we have included a description of the naphthyridine precursors, intermediates, and target drugs prepared via this alternative synthetic procedure.

Formation of 4,6-Dichloro-1,5-Naphthyridine

As described in the preceding section, we have already prepared and characterized the key intermediate, 4,6-dichloro-1,5-naphthyridine (NI-23), as a by-product in the chlorination of several 6-alkoxy-4-hydroxy-1,5-naphthyridines.

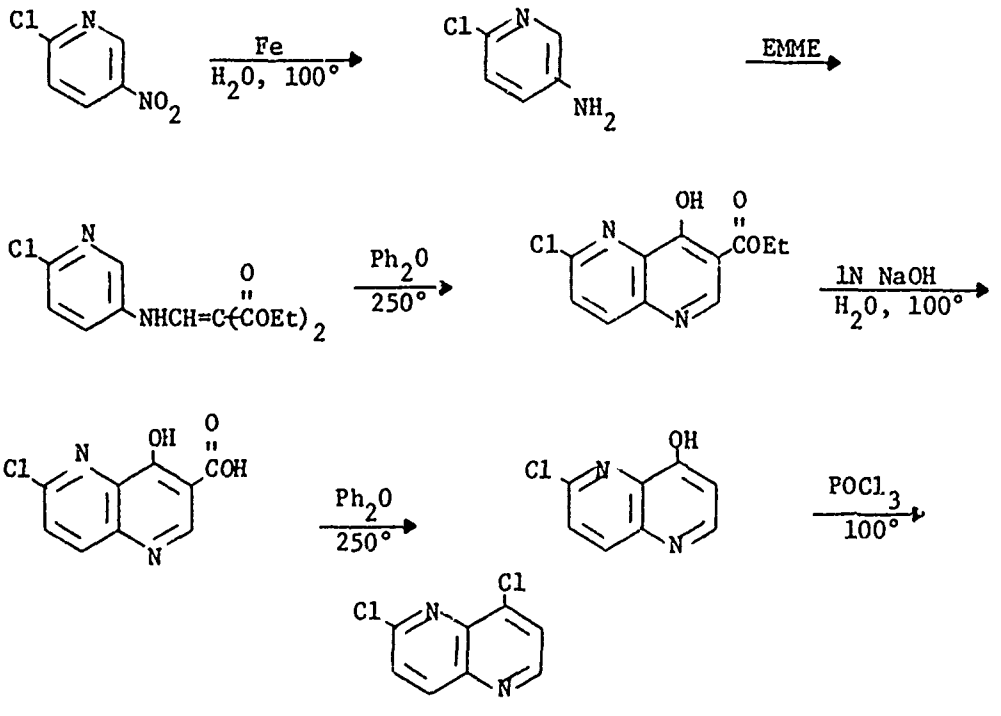


(NI-23)

However, both the low and variable yields of NI-23 as prepared via this route could preclude its use as a valuable synthetic intermediate. We have therefore successfully applied the EMME procedure to 3-amino-6-chloropyridine as disclosed in Scheme 2 as an alternate route to 4,6-dichloro-1,5-naphthyridine. The analytical data for the naphthyridine precursors and intermediates prepared via Scheme 2 are included in Table 8 at the end of this section.

Scheme 2

Formation of 4,6-Dichloro-1,5-Naphthyridine



(NI-23)

Starting from the commercially available 2-chloro-5-nitropyridine, 3-amino-6-chloropyridine (NP-25) was prepared via the reported technique employing iron in water solution (18). We have noted that greatly increased yields can be achieved in this reduction by running the reaction at 100° instead of the lower temperatures as reported. In the second step, diethyl 6-chloro-3-pyridylamino-methylenemalonate (NP-26) was obtained in nearly quantitative yield by reaction of 3-amino-6-chloropyridine with ethoxymethylenemalonic ester. The proton spectrum of pure NP-26 is reproduced in Figure 23, and is clearly in accord with the structure as formulated.

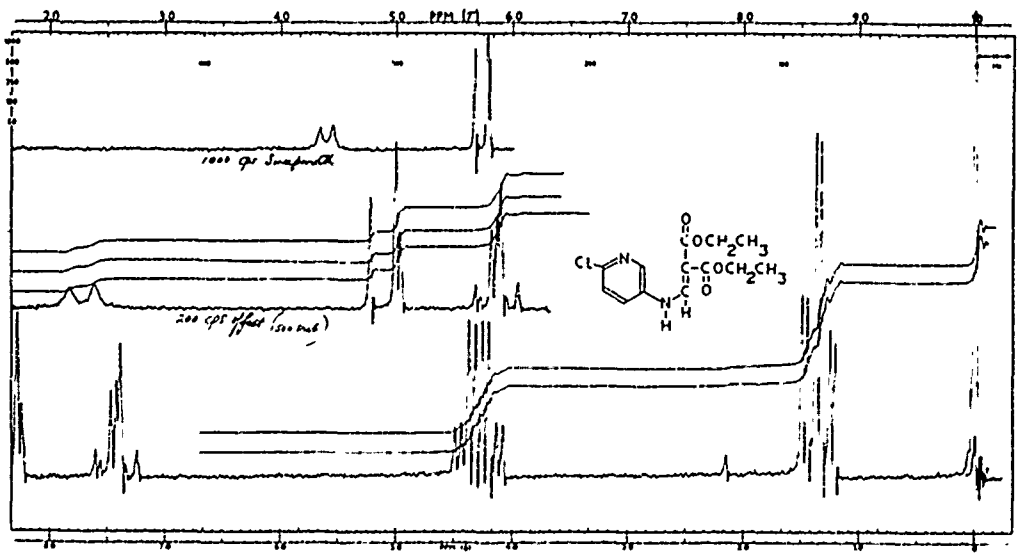
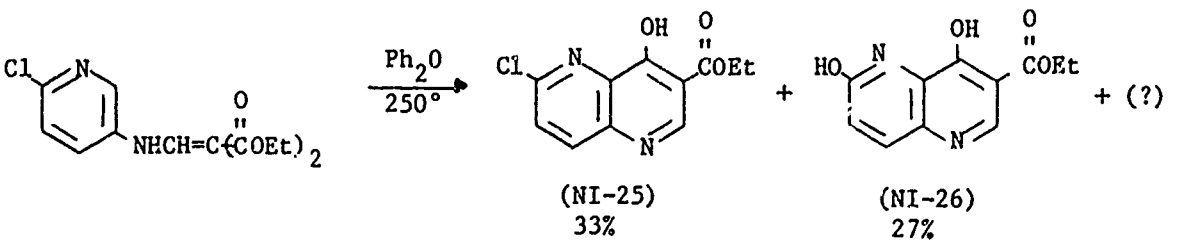


Figure 23. Proton spectrum of diethyl 6-chloro-3-pyridylaminomethylenemalonate ($CDCl_3$)

In the next step, thermal cyclization to the 1,5-naphthyridine did not proceed as straightforward as depicted in Scheme 2. Instead, a mixture of at least three different components was observed.



(NI-25) 33%

(NI-26) 27%

As shown above, to date we have succeeded in separating the predicted 6-chloro ester (NI-25) and, somewhat surprisingly, the 6-hydroxy ester (NI-26) in roughly equivalent yields of 30%. A possible explanation for the formation of the 6-hydroxy ester is the following. An intermediary

6-ethoxy ester (formed by reaction of the ethanol produced in the cyclization with the 6-chloro ester, NI-25) is cleaved at the ether linkage in the presence of the hydrogen chloride at 250°. The third component, an intractable brown powder, has presently eluded all attempts at its characterization. The infrared spectra for the 6-chloro and 6-hydroxy esters are reproduced in Figures 24 and 25, respectively. As seen for the 6-hydroxy ester (Figure 25) the shoulder at 5.93μ is consistant with the predicted tautomeric keto structure which should be preferred in the solid state (19).

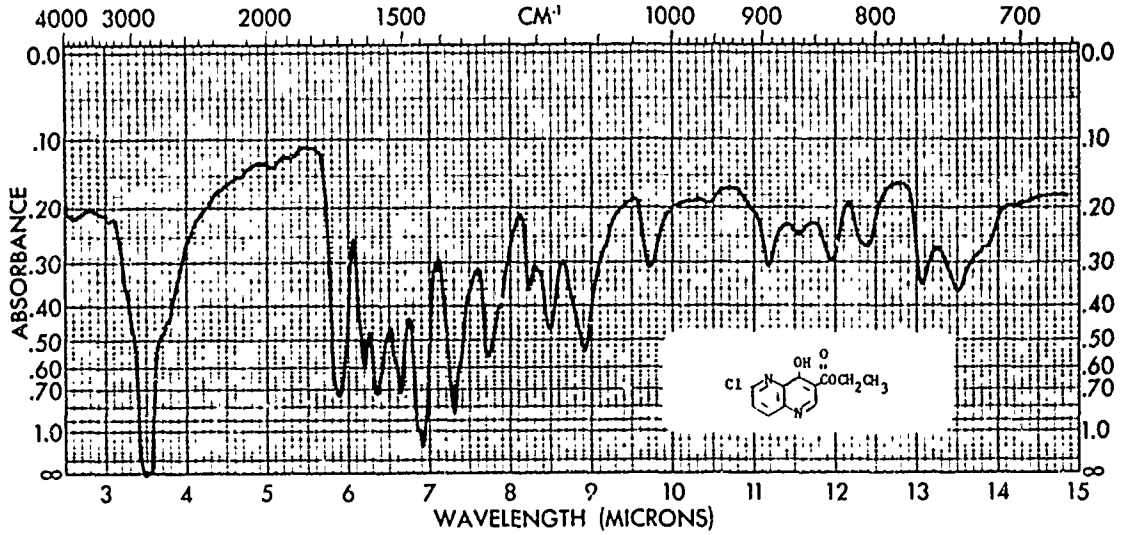


Figure 24. Infrared spectrum of 3-carbethoxy-6-chloro-4-hydroxy-1,5-naphthyridine (nujol mull).

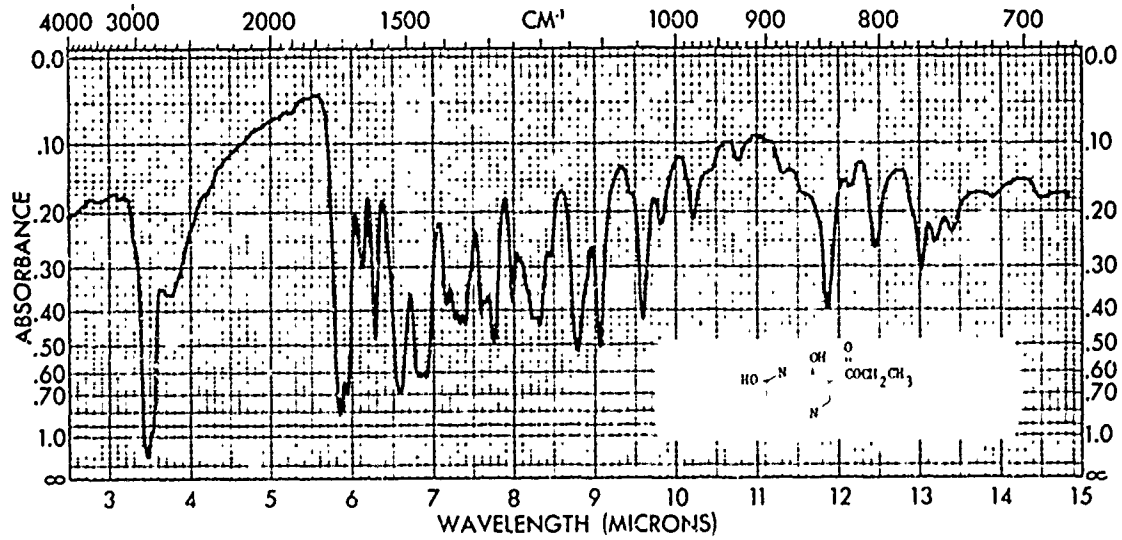
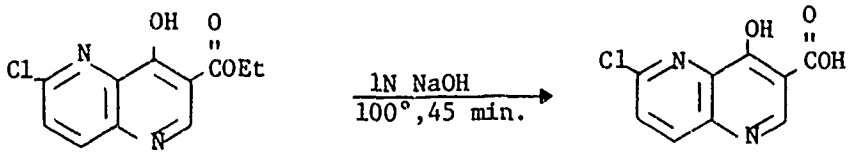


Figure 25. Infrared spectrum of 3-carbethoxy-4,6-dihydroxy-1,5-naphthyridine (nujol mull).

While either of these two esters (NI-25 or NI-26) could be carried through the remaining steps in Scheme 2 to afford the key intermediate, we have first chosen to prove the applicability of this route with the 6-chloro ester (NI-25). Accordingly, the hydrolysis of the ester group of NI-25 was conducted in normal sodium hydroxide at reflux.



In this saponification step, heating was continued for as short a period as possible to avoid complications arising from concurrent hydrolysis of the 6-chlorine atom. The product, 3-carboxy-6-chloro-4-hydroxy-1,5-naphthyridine (NI-27) was then conveniently isolated by acidification of the reaction medium. The infrared spectrum for this acid is reproduced in Figure 26, and discloses the predicted carbonyl absorption at 5.92μ

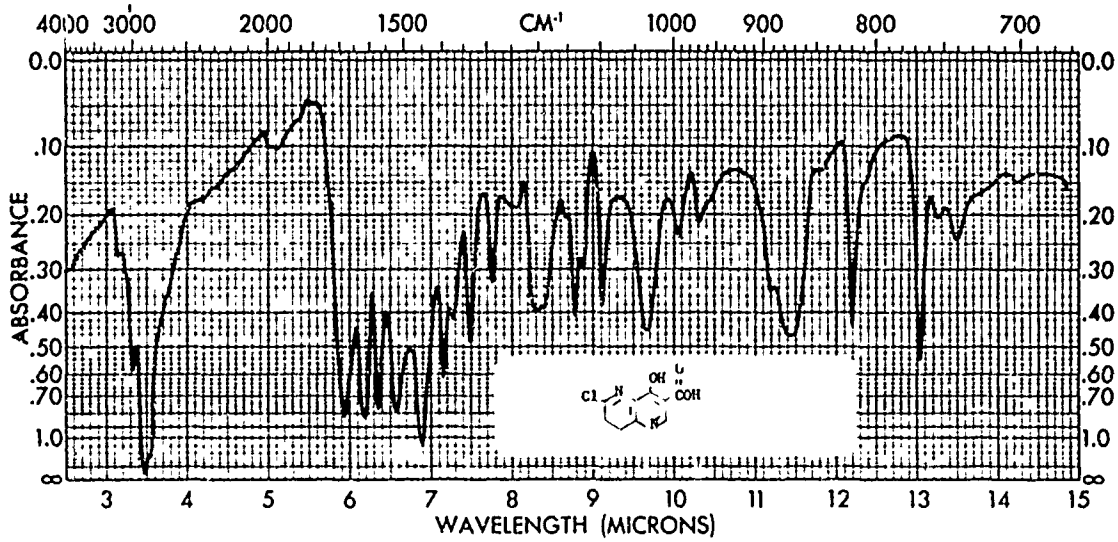
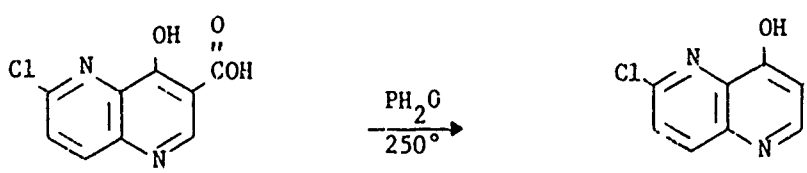
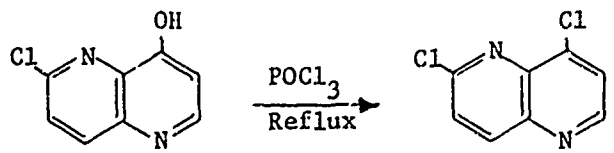


Figure 26. Infrared spectrum of 3-carboxy-6-chloro-4-hydroxy-1,5-naphthyridine (nujol mull).

In the next step of Scheme 2, thermal decarboxylation of this acid was first attempted in refluxing diphenyl ether.



At this stage, we noted that while some decarboxylation occurs, higher temperatures are required since a substantial carbonyl peak at 5.9 μ was observed in the crude product. We have recently noted that this decarboxylation can be driven to completion by running the reaction in nujol at 280-300°. In the succeeding step as shown in Scheme 2, reaction of the crude 6-chloro-4-hydroxy-1,5-naphthyridine with refluxing phosphorus oxychloride afforded the key intermediate, 4,6-dichloro-1,5-naphthyridine, in low yield after the usual work-up.



The analytical data for this dichloro derivative are included in Table 8. The proton spectrum is reproduced in Figure 27 and was identical to the analytical sample (see Experimental). The presence of four sets of doublets at low field is consistent solely with the structure as formulated. The small peak near 7.8 τ is a solvent impurity and was not present in the analytical sample.

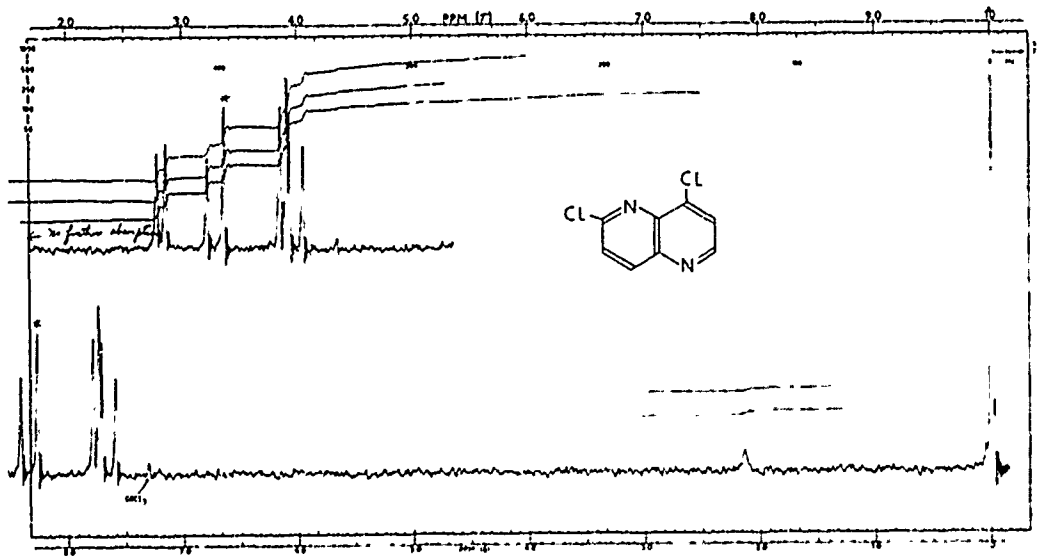
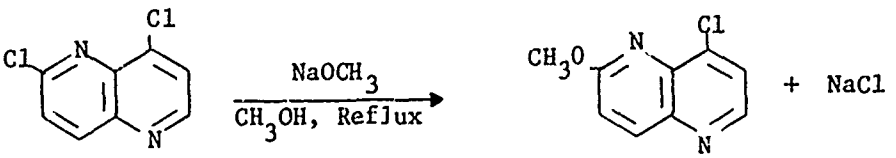


Figure 27. Proton spectrum of 4,6-dichloro-1,5-naphthyridine ($CDCl_3$).

Formation of 6-Alkoxy-4-Chloro-1,5-Naphthyridines

The succeeding step as delineated in Scheme 2 above, the introduction of alkoxy functionality into the 6-position of 4,6-dichloro-1,5-naphthyridine, was then conducted in the following manner. A mixture of 4,6-dichloro-1,5-naphthyridine and one mole-equivalent of sodium methoxide was slowly brought to reflux. The rapid appearance of a suspension of the inorganic by-product served as a clear indication for the completion of the reaction.



Solvent was then removed, and the resultant solid sublimed at 80-100° (0.04 mm) to afford analytically pure (Table 8), 4-chloro-6-methoxy-1,5-naphthyridine as a white powder in 88% yield. The proton spectrum for this intermediate is reproduced in Figure 28, and clearly demonstrates that the methoxy group has been selectively introduced into the ring-6 position to the complete exclusion of attack at the 4-position. In addition to a methoxy singlet present at 5.9 τ, the four doublets observed at 1-3 τ are characteristic for a 4,6-disubstituted-1,5-naphthyridine. Also, the resonance of the ring-7 hydrogen (2.9 τ) has shifted upfield from the corresponding proton in the starting material (2.3 τ). The magnitude of this shift agrees well with the 0.6 τ upfield shift observed for the ring-3 proton upon substitution of a methoxy group for the 2-chlorine atom present in 2,4-dichloro-1,5-naphthyridine (2). Also, the chemical shift of the corresponding ring-7 hydrogen atom present in 6-n-butoxy-4-chloro-1,5-naphthyridine (3.0 τ) confirms the point of attachment, since this analog was prepared via an alternative and unabiguous procedure as described in Section 3.1.1.

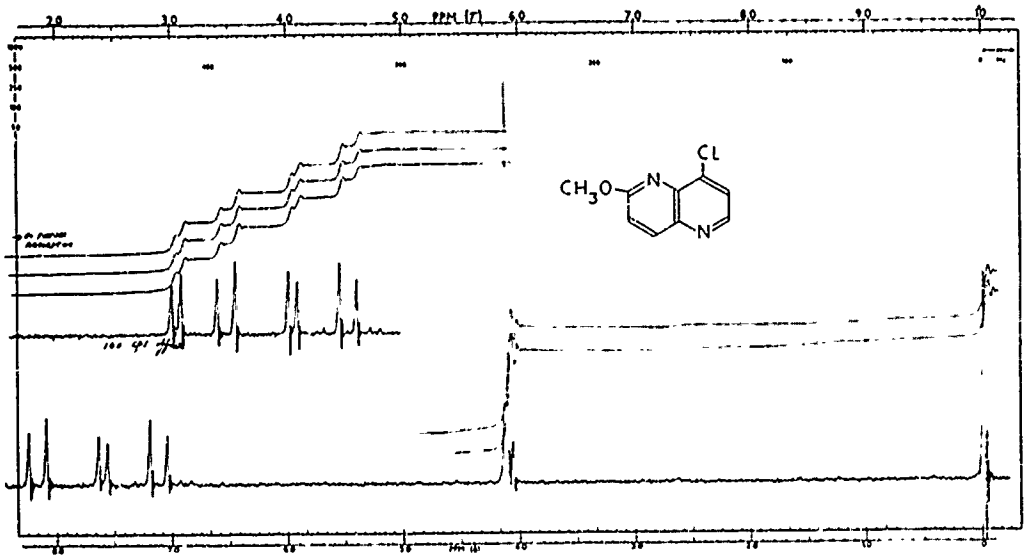
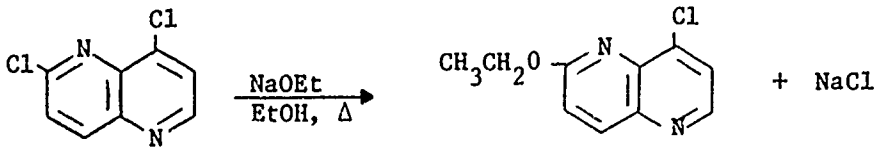
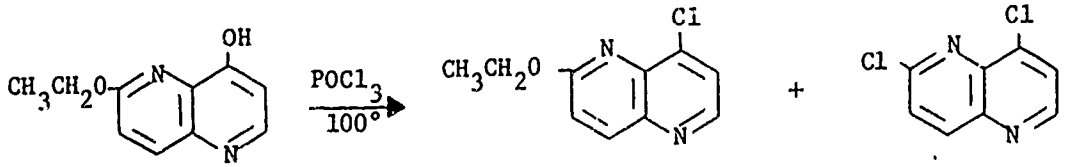


Figure 28. Proton spectrum of 4-chloro-6-methoxy-1,5-naphthyridine ($CDCl_3$)

To date, we have confirmed the generality of this procedure by the corresponding reaction employing ethoxide as the attacking nucleophile.



The product, 4-chloro-6-ethoxy-1,5-naphthyridine (NI-29), was isolated in high yield, and its proton spectrum is reproduced in Figure 29. This material exhibited both physical and spectral characteristics identical to the product obtained via the conventional EMME route (see Experimental). However, as has been previously discussed, a complication of the latter route proved to be the generation of a difficulty separable mixture of both 4-chloro-6-ethoxy-1,5-naphthyridine (NI-29) and 4,6-dichloro-1,5-naphthyridine (NI-23).



(50:50 Mixture)

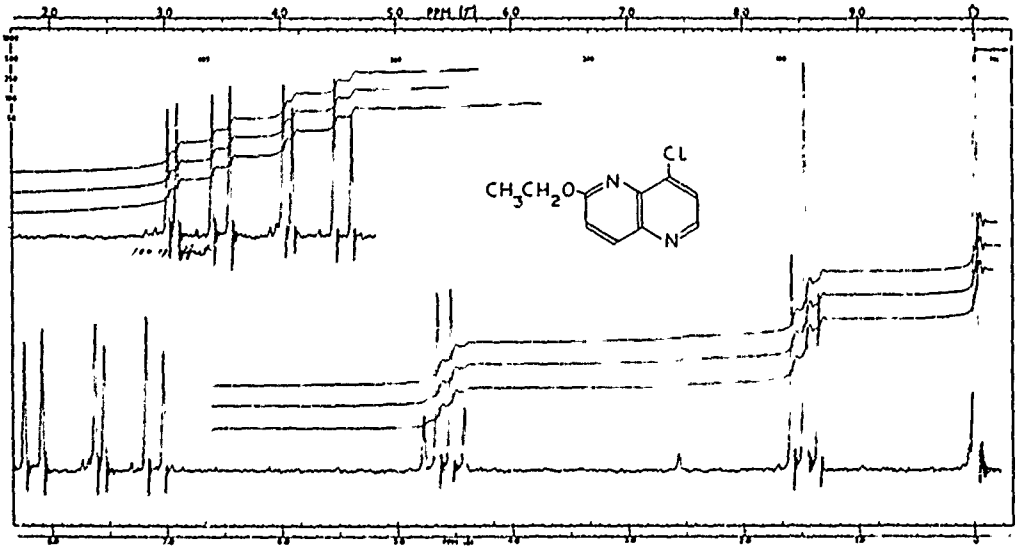


Figure 29. Proton spectrum of 4-chloro-6-ethoxy-1,5-naphthyridine ($CDCl_3$)

Table 8

6-Alkoxy-1,5-Naphthyridine Intermediates and Precursors

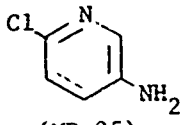
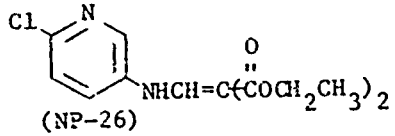
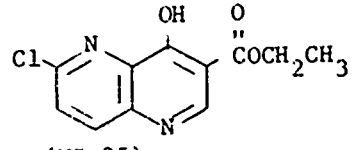
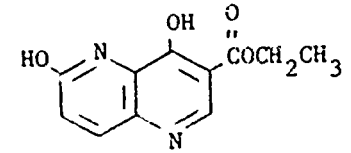
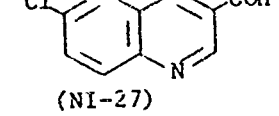
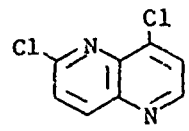
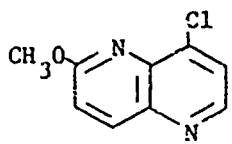
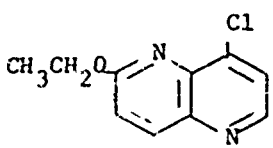
Structure	M.P., °C	Elemental Analysis			
		C	H	N	
 (NP-25)	81-82	46.71 46.84	3.92 3.93	21.79 21.93	Theory Found
 (NP-26)	127-128	52.26 52.37	5.06 5.11	9.38[a] 9.45	
 (NI-25)	300-302[b]	52.29 52.57	3.59 3.57	11.09 11.22	
 (NI-26)	294-295°	56.41 56.58	4.30 3.73	11.96 11.93	
 (NI-27)	>310°	48.12 48.18	2.24 2.36	12.47 12.88	

Table 8 (Cont'd.)

Structure	M.P., °C	Elemental Analysis		
		C	H	N
 (NI-23)	153-154	48.27 48.48	2.02 2.23	14.08[c] 14.56
 (NI-28)	93-94	55.54 55.85	3.63 3.69	14.40[d] 14.32
 (NI-29)	60-61	57.56 57.28	4.35 4.27	13.43 13.74

(a) Theory for Cl = 11.87; Found = 11.80.

(b) Converts from dark gray to a white solid at 245-250°.

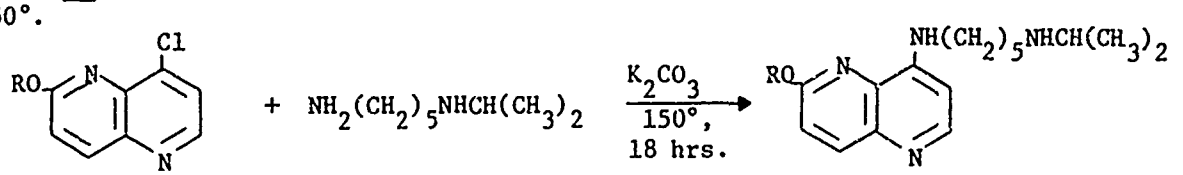
(c) Theory for Cl = 35.63; Found = 35.00.

(d) Theory for Cl = 18.22; Found = 17.90.

6-Alkoxy-4-Amino-1,5-Naphthyridines

The title derivatives which were prepared via our modified EMME procedure are included in Table 9 at the end of this section along with their physical constants and full analytical data.

The reaction of both 4-chloro-6-methoxy-1,5-naphthyridine (NI-28) and 4-chloro-6-ethoxy-1,5-naphthyridine (NI-29) with 5-isopropylaminopentylamine (13) was conducted employing an excess of the diamine as solvent at 150°.



R = CH_3, CH_3CH_2

The potassium carbonate served as an acid scavenger for the hydrogen chloride generated in the reaction which conceivably could catalyze the migration of the alkyl groups from the ether linkage to the ring-5 nitrogen (2). Both products were isolated in 50-60% yields by molecular distillation. The analytical data are included in Table 9 at the end of this section, and the proton spectra for both the 6-methoxy- and 6-ethoxy-products (NT-11 and NT-12) are reproduced in Figures 30 and 31 respectively.

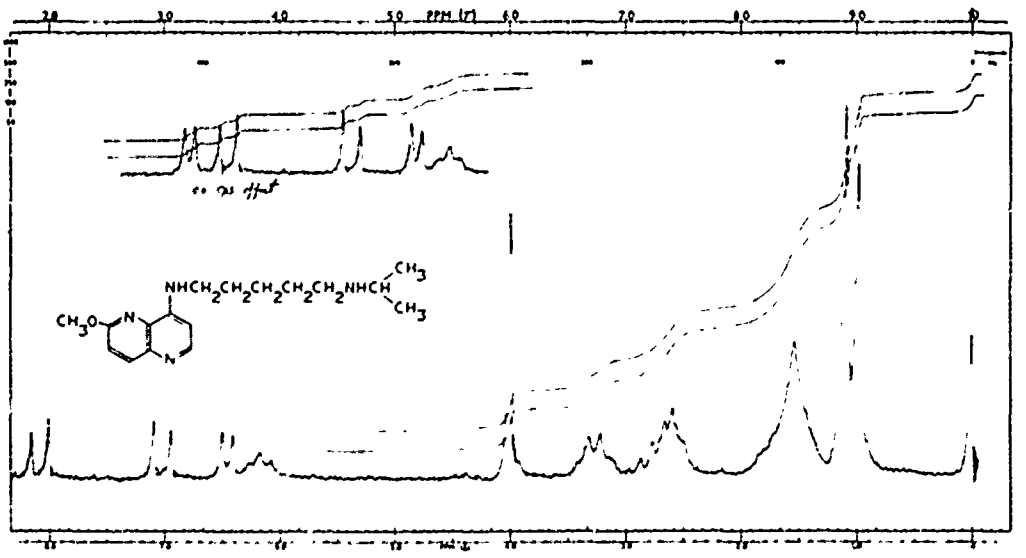


Figure 30. Proton spectrum of 6-methoxy-4-(5-isopropylaminopentylamino)-1,5-naphthyridine ($CDCl_3$).

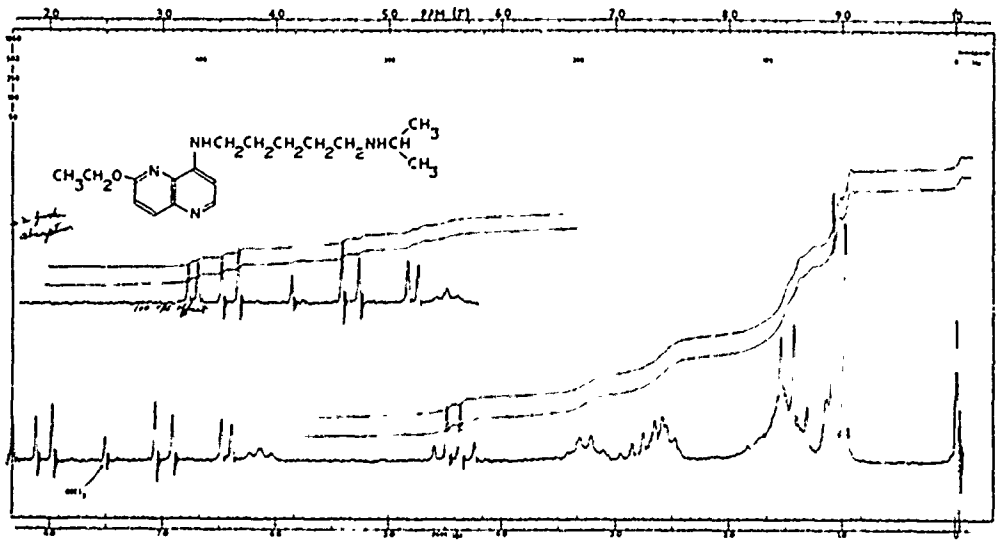
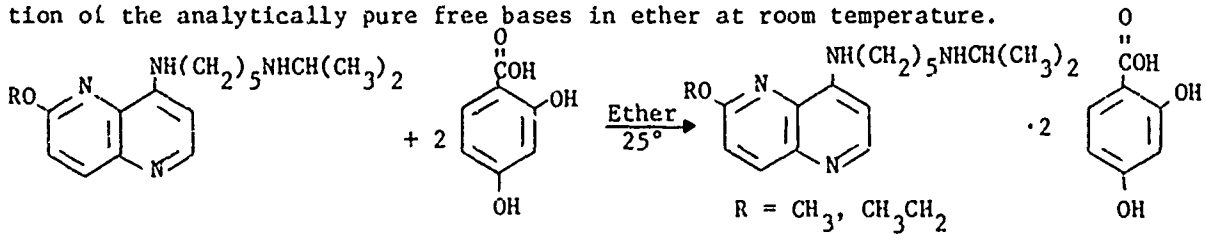


Figure 31. Proton spectrum of 6-ethoxy-4-(5-isopropylaminopentylamino)-1,5-naphthyridine ($CDCl_3$).

As we have discussed previously in this report, the appearance of a broad triplet near 4.0τ for the 4-amino proton coupled with a clean doublet near 9.0τ for the isopropyl group proves that the point of attachment of the pentaquine side chain is as formulated. The noticeable shoulder at 8.86τ on the isopropyl doublet in the 6-ethoxy derivative (Figure 31), however, may be ascribable to a slight impurity of the side-chain retroisomer. At present, we cannot discount this possibility. Also, the presence of noticeable absorptions near 6.0μ in the infrared spectra of the forecuts of these molecular distillations may be a result of alkyl group migration from the 6-position to the ring-5 nitrogen as discussed above.

Conversion of both NT-11 and NT-12 to their di-β-resorcylate salts was conducted in ether at room temperature. Experimentally, a slight excess of β-resorcylic acid in ether solution was slowly added into a solution of the analytically pure free bases in ether at room temperature.



Both products, NT-13 and NT-14, immediately separated from solution and were isolated as analytically pure, white solids after filtration, washing with ether, and drying under vacuum at room temperature. The analytical data are included in Table 9, and the infrared spectrum for the 6-methoxy salt is reproduced in Figure 32. As predicted, the infrared spectrum for the 6-ethoxy salt was virtually superimposible upon this spectrum.

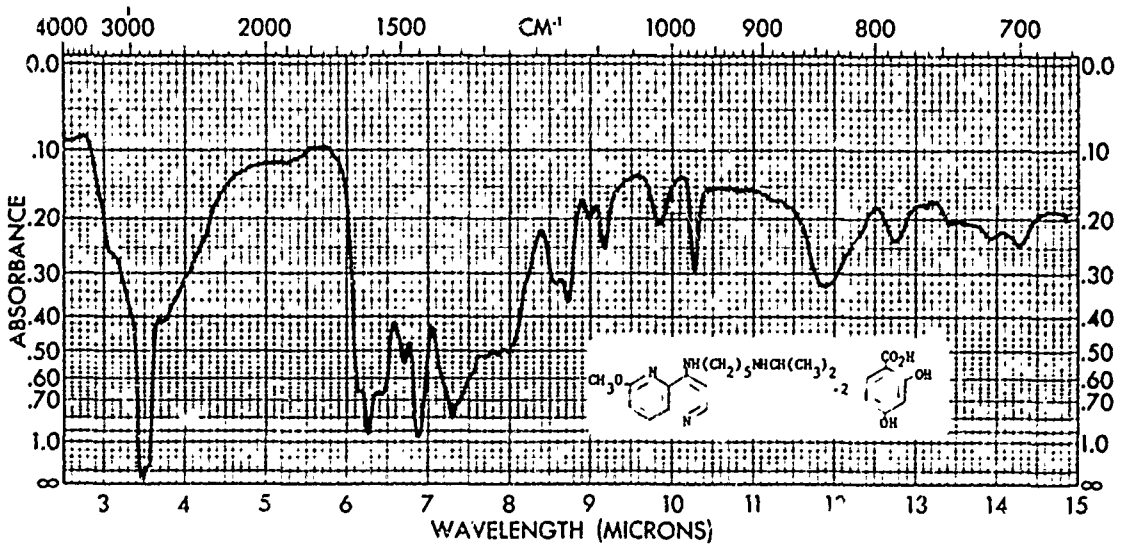
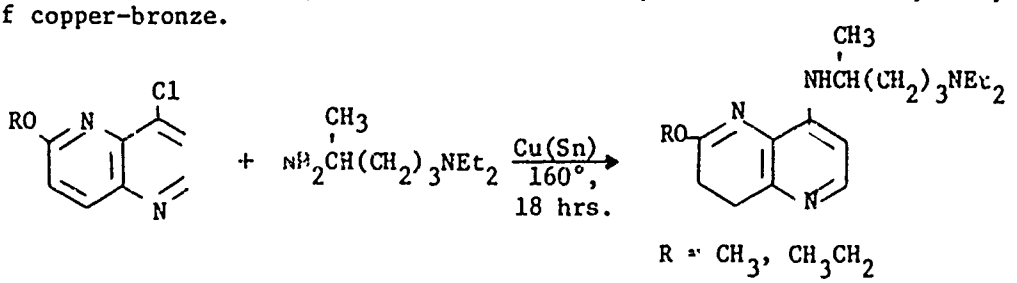


Figure 32. Infrared spectrum of 6-methoxy-4-(5-isopropylaminopentylamino)-1,5-naphthyridine di-β-resorcylate (nujol mull).

The introduction of the pamaquine side chain was conducted in an analogous fashion. Both 4-chloro-6-methoxy-1,5-naphthyridine (NI-28) and 4-chloro-6-ethoxy-1,5-naphthyridine (NI-29) were reacted with an excess of 2-amino-4-diethylaminopentane at 160° in the presence of a catalytic quantity of copper-bronze.



R = CH_3, CH_3CH_2

In both instances, it was noted that considerable amounts of unreacted starting material were present even after eighteen hours at 160°. Nevertheless, both of these products could be isolated by molecular distillation in sufficient yield for biologic testing. It is of interest to note that the synthesis of the 6-methoxy-4-(4-diethylamino-1-methylbutylamino)-1,5-naphthyridine (NT-15) was originally attempted by Goldberg nearly twenty years ago (5); however, difficulties encountered in the conventional EMME procedure precluded its formation. Full analytical data for both NT-15 and NT-18 are included in Table 9, and the proton spectra for both of these derivatives are reproduced in Figures 33 and 34, respectively.

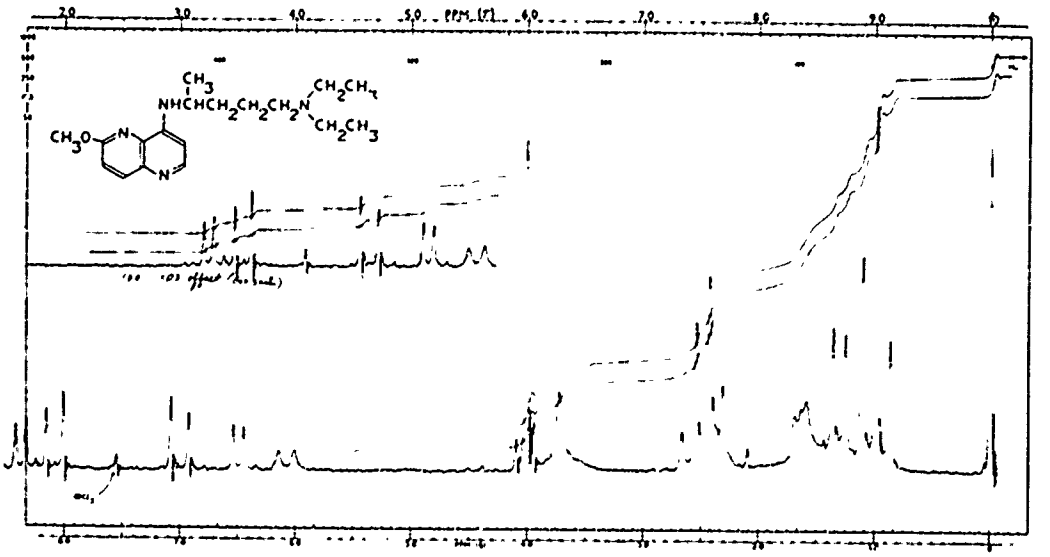


Figure 33. Proton spectrum of 6-methoxy-4-(4-diethylamino-1-methylbutylamino)-1,5-naphthyridine ($CDCl_3$).

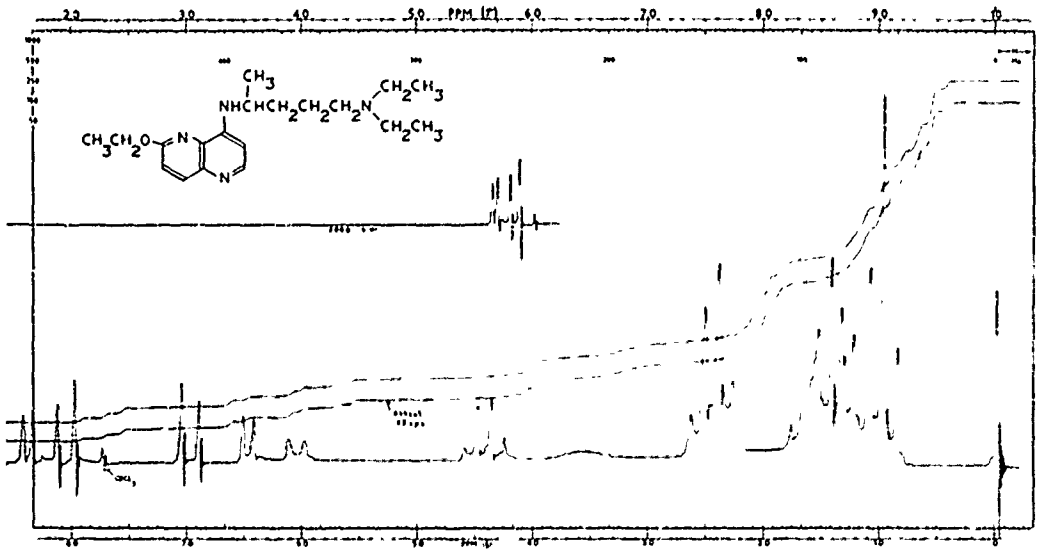
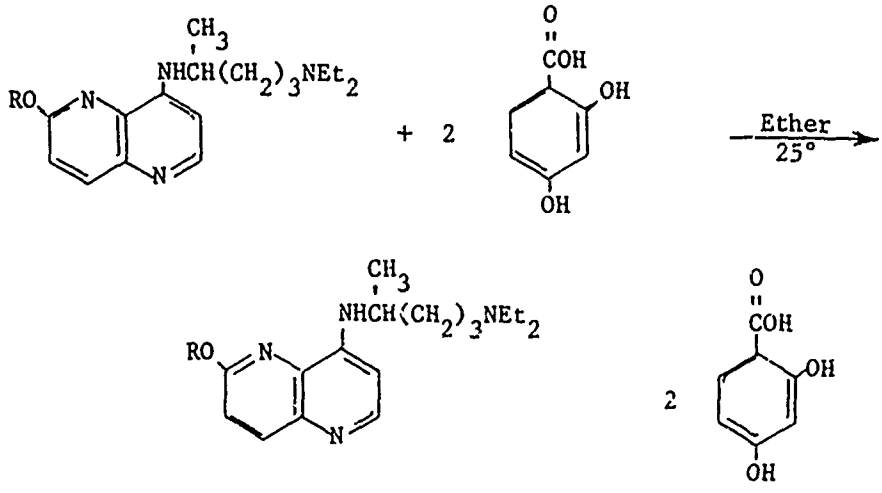


Figure 34. Proton spectrum of 6-ethoxy-4-(4-diethylamino-1-methylbutylamino)-1,5-naphthyridine ($CDCl_3$).

The di-β-resorcylate salts of both NT-15 and NT-18 were prepared via our usual technique in ether at room temperature.



R = CH_3, CH_3CH_2

The analytical data for both of these derivatives are included in Table 9. The 6-methoxy analog (NT-16) consistently analyzed for a mono-hydrate. Its infrared spectrum is reproduced in Figure 35 and was virtually superimposible upon that of the 6-ethoxy salt (NT-19).

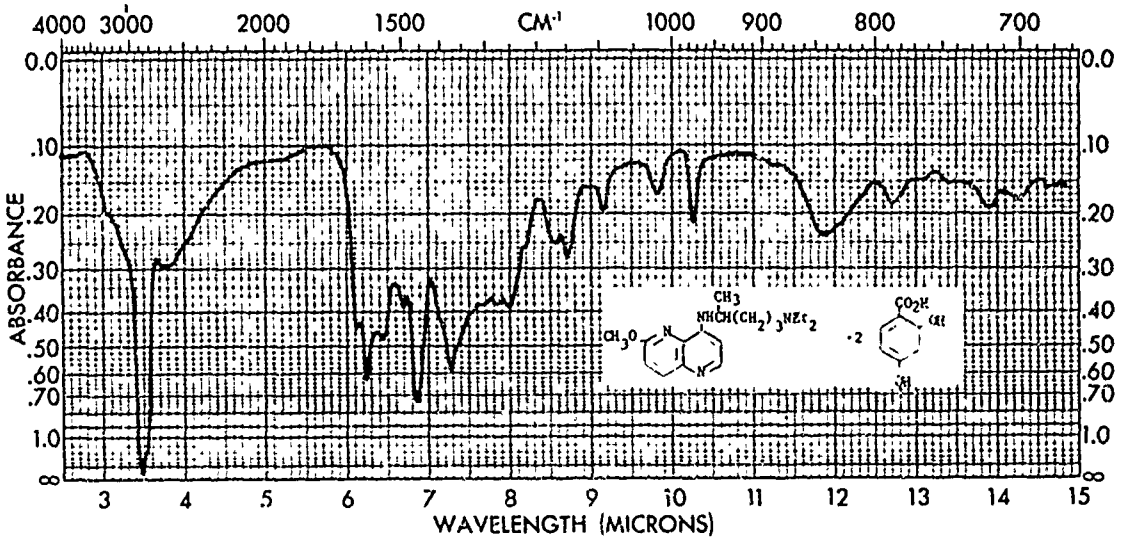


Figure 35. Infrared spectrum of 6-methoxy-4-(4-diethylamino-1-methylbutylamino)-1,5-naphthyridine di-β-resorcylate mono-hydrate (nujol mull).

Table 9

6-Alkoxy-4-Amino-1,5-Naphthyridines

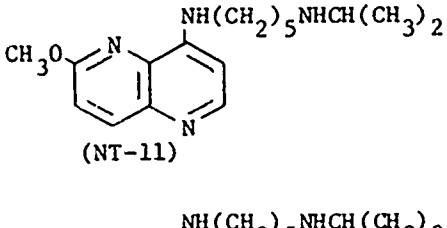
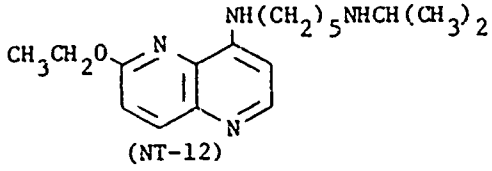
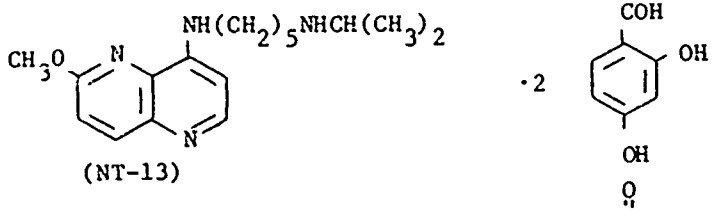
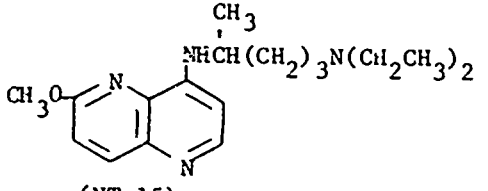
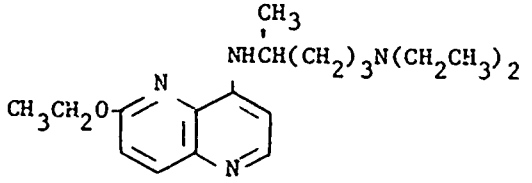
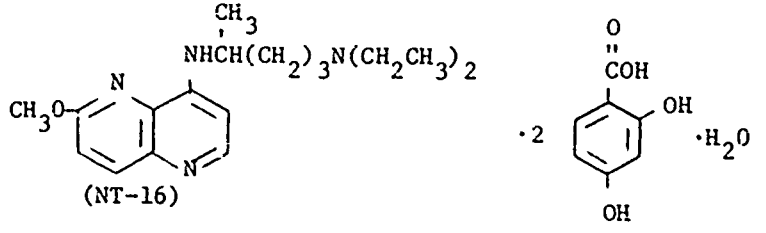
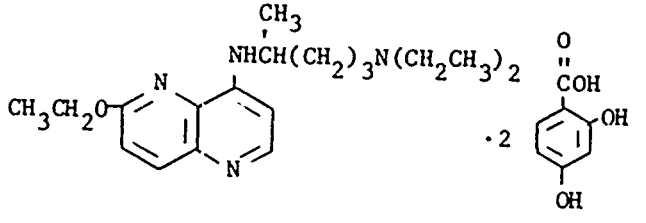
Structure	M.P., °C / B.P., °C (mm)	Elemental Analysis C	H	N	
 (NT-11)	140-145(0.01) [a]	67.51 67.87	8.67 8.85	18.53 18.33	Theory Found
 (NT-12)	160-175(0.08) [a]	68.32 67.96	8.92 9.15	17.71 18.08	
 (NT-13)	103-105	60.97 60.60	6.27 6.61	9.18 9.45	
(NT-14)	96-98	61.52 61.26	6.45 6.93	8.97 8.91	

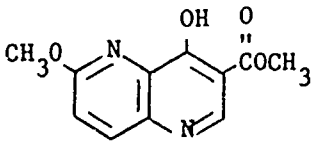
Table 9 (Cont'd.)

Structure	M.P., °C B.P., °C(mm)	Elemental Analysis C	 H	 N
 (NT-15)	125-130(0.07) (a)	68.32 68.62	8.92 9.18	17.71 17.66
 (NT-18)	130-150 (0.05) (a)	69.05 69.47	9.15 9.17	16.96 16.52
 (NT-16)	98-100	59.80 59.83	6.59 6.61	8.72 8.82
 (NT-19)	90-93	62.05 61.89	6.63 6.89	8.87 8.69

(a) Molecular distillation.

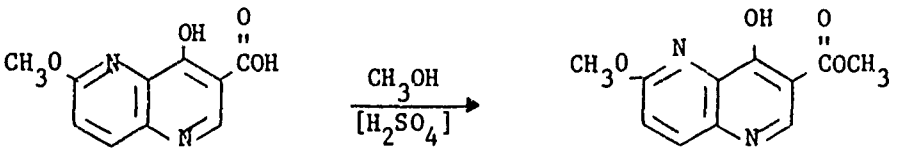
3.1.3 6-Methoxy-3-Carbomethoxy-4-Hydroxy-1,5-Naphthyridines

Early in this program, we submitted several 6-alkoxy-3-carboethoxy-4-hydroxy-1,5-naphthyridines to WRAIR. These compounds were prepared as intermediates; however, the contract monitor pointed out the similarity of these compounds to certain 4-hydroxyquinolines which have been recently reported to exhibit both suppressive and prophylactic activity at extremely low dosage levels (15,20). It was agreed that the 6-methoxy-3-carbomethoxy-4-hydroxy-1,5-naphthyridine,



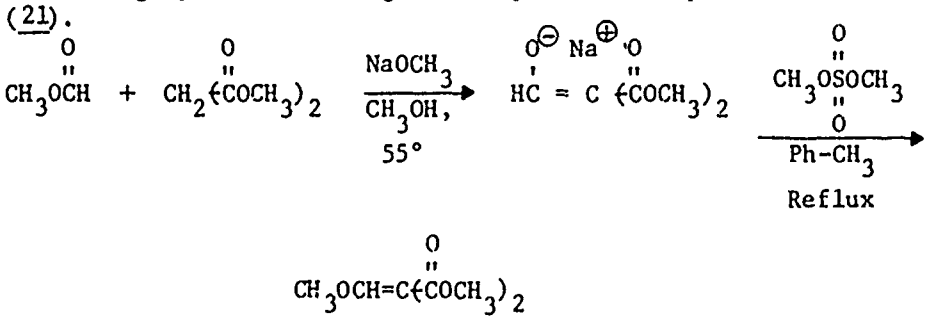
would be the most interesting member of this class. Accordingly, we applied our synthetic efforts to the formation of this specific compound.

Our first approach involved the methanolysis of our previously characterized 3-carboxy-4-hydroxy-6-methoxy-1,5-naphthyridine (NI-7).

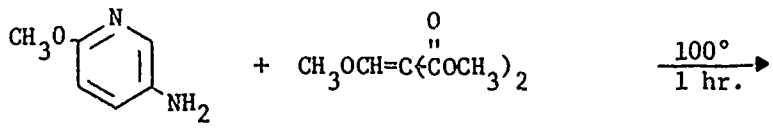


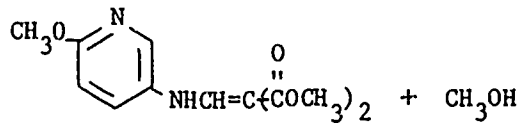
This approach was abandoned, however, since no pure component could be isolated from the reaction mixture. Presumably, the high degree of insolubility of the starting acid in the reaction medium proved to be the limiting factor.

Our second approach was more rewarding, and involved the use of dimethyl methoxymethylenemalonate in place of the diethyl ethoxymethylenemalonate in the conventional EMME synthesis. This starting material was prepared in high yield according to the procedure reported in the literature (21).



As predicted, the analytically pure material (Table 10) exhibited three methoxy singlets (6.03τ, 6.24τ and 6.30τ) in addition to the vinylic singlet present at 2.40τ ($CDCl_3$). The reaction of this precursor with 3-amino-6-methoxypyridine was then conducted via our standard procedure.





The yield of crude product, dimethyl 6-methoxy-3-pyridylamino-methylenemalonate (NP-28) was virtually quantitative. However, it was absolutely essential that this material be extremely pure before conducting the next step. The proton spectrum for the analytically pure material (Table 10) is reproduced in Figure 36, and clearly exhibits the predicted resonances.

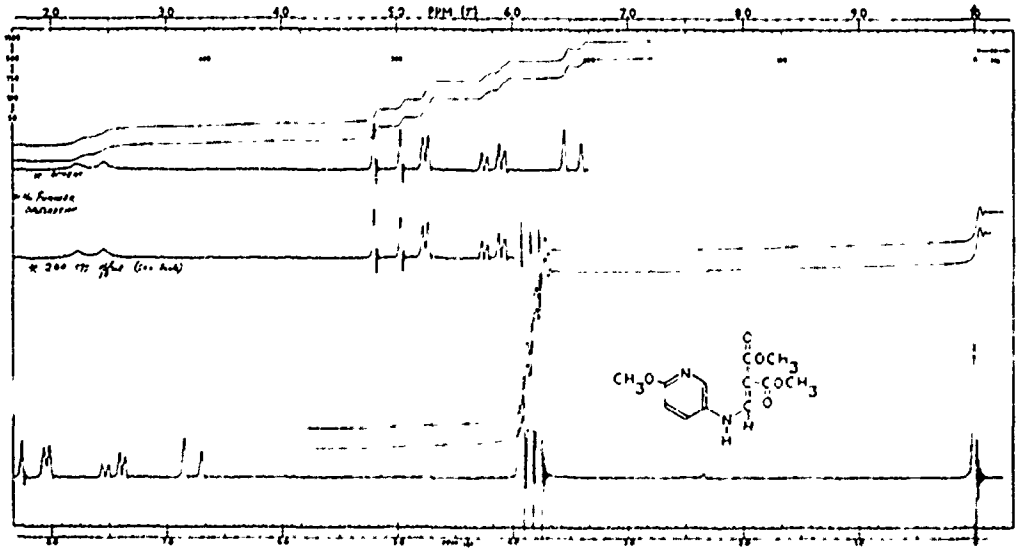
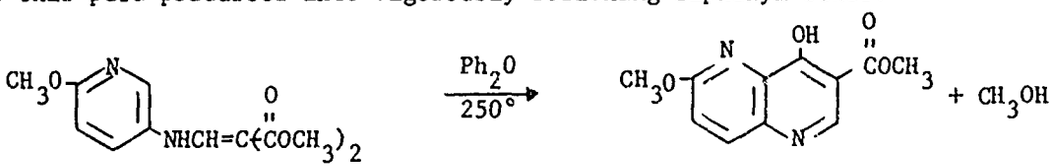


Figure 36. Proton spectrum of dimethyl 6-methoxy-3-pyridylaminomethylene-malonate ($CDCl_3$).

The cyclization of NP-28 was then conducted by the slow addition of this pure precursor into vigorously refluxing diphenyl ether.



The product, 3-carbomethoxy-4-hydroxy-6-methoxy-1,5-naphthyridine (NT-17), separated from solution in quantitative yield upon cooling. The analytical sample (Table 10) was obtained as an off-white powder after repeated trituration with hot ethanol. The infrared spectrum (Figure 37) exhibits two absorptions in the carbonyl region. The peak at 5.86μ is ascribed to the ester absorption, and the peak at 5.97μ may be assigned to the naphthyridone tautomeric form (19).

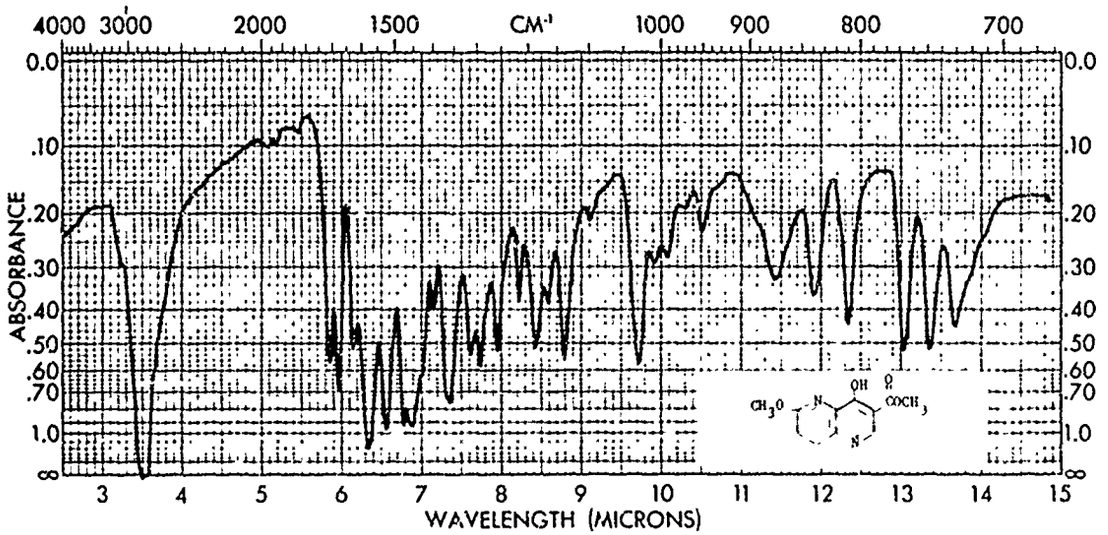
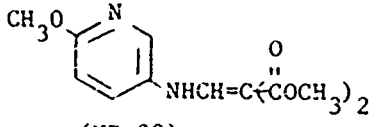
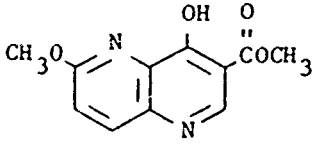


Figure 37. Infrared spectrum of 3-carbomethoxy-4-hydroxy-6-methoxy-1,5-naphthyridine (nujol mull).

It should be mentioned that when the ring cyclization was attempted using either crude acrylate (NP-28) or via direct heating of 3-amino-6-methoxypyridine with dimethyl methoxymethylenemalonate in diphenyl ether. extensive decomposition occurred to afford a black, intractable solid. The use of absolutely pure acrylate as described above, however, proceeded without any difficulties.

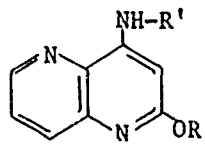
Table 10

6-Alkoxy-3-Carboalkoxy-4-Hydroxy-1,5-Naphthyridines

Structure	M.P.,°C	Elemental Analysis C	H	N	
$CH_3OCH=C(COCH_3)_2$ (NP-27)	36-39	48.27 47.95	5.79 5.84	0.00 --	Theory Found
 (NP-28)	138-140	54.13 54.05	5.30 5.32	10.52 10.74	
 (NT-17)	288-290	56.41 56.42	4.30 4.31	11.96 11.82	

3.2 2-Alkoxy-4-Amino-1,5-Naphthyridines

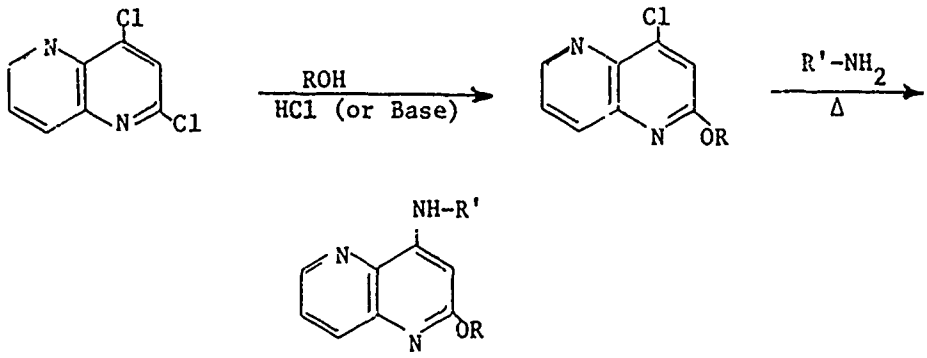
As stated earlier in this report, our second main area of research involved the synthesis of selected 2-alkoxy-4-amino-1,5-naphthyridines of the following general structure:

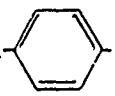
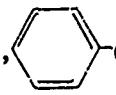


Target drugs of this type may be viewed upon as being the "5-Aza" isosteres of the highly active 8-aminoquinolines, pamaquine, pentaquine and primaquine. Our primary synthetic route to these derivatives is illustrated in Scheme 3 below.

Scheme 3

Synthetic Route to 2-Alkoxy Analogs



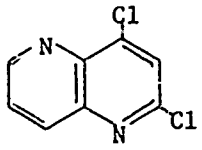
R = H, CH_3, Cl-  -CH_2,  -CH_2, CF_3CH_2 [also, OR = Cl and NH_2 via variations of this scheme (22)].

R' = $C(CH_2)_3NEt_2$, $CH(CH_2)_3NH_2$, $(CH_2)_5NHCH(CH_3)_2$.

In the subsections below, we have discussed in turn: (1) the procedures used to prepare the key intermediate, 2,4-dichloro-1,5-naphthyridine; (2) the formation of the 2-alkoxy-4-chloro-1,5-naphthyridine intermediates; and (3) the preparation of the target 2-alkoxy-4-amino-1,5-naphthyridines.

3.2.1 Preparation of the Key Intermediate: 2,4-Dichloro-1,5-Naphthyridine

The formation of the key intermediate, 2,4-dichloro-1,5-naphthyridine,



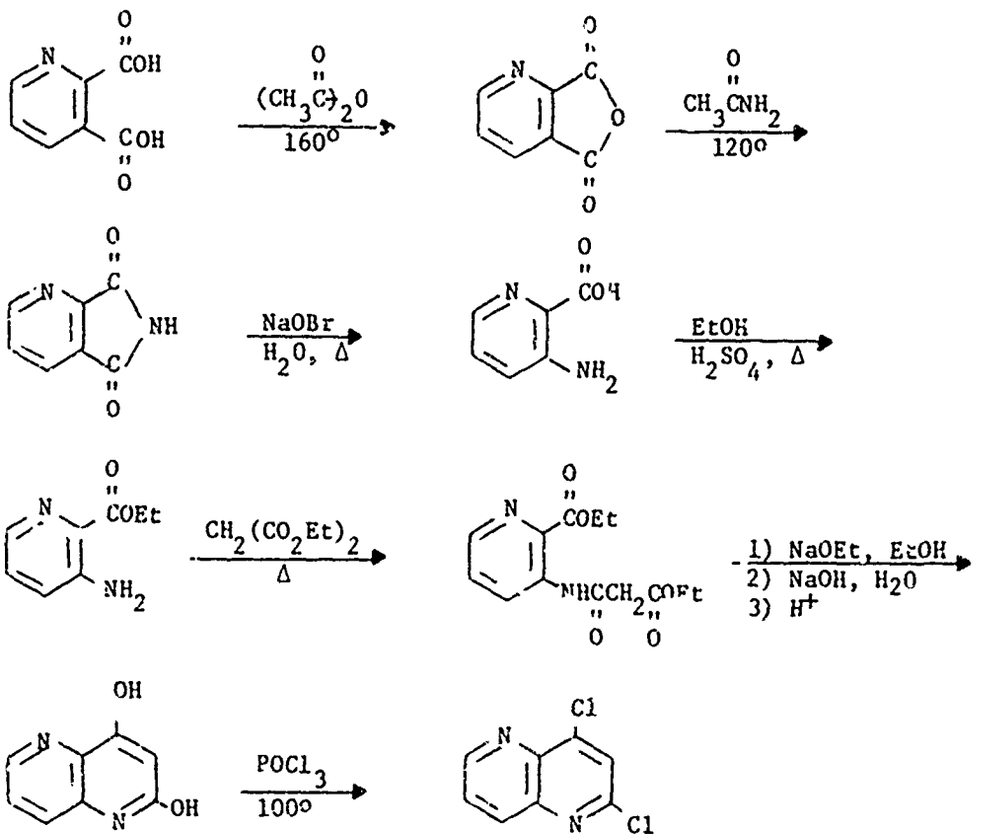
was performed via two routes. The first procedure is described immediately below and essentially follows the method as reported in the literature (23). Our second, and improvised route to this key intermediate involved a Meisenheimer reaction as applied to 4-chloro-1,5-naphthyridine-1-N-oxide. The latter route is more amenable to side-up and is several steps shorter than the conventional procedure.

Conventional Route to 2,4-Dichloro-1,5-Naphthyridine

Oakes and Rydon (23) have reported the formation of 2,4-dichloro-1,5-naphthyridine by a procedure which is based upon the well-known von Niementowski synthetic scheme (24). The essential features of Oakes and Rydon's procedure are outlined in Scheme 4.

Scheme 4

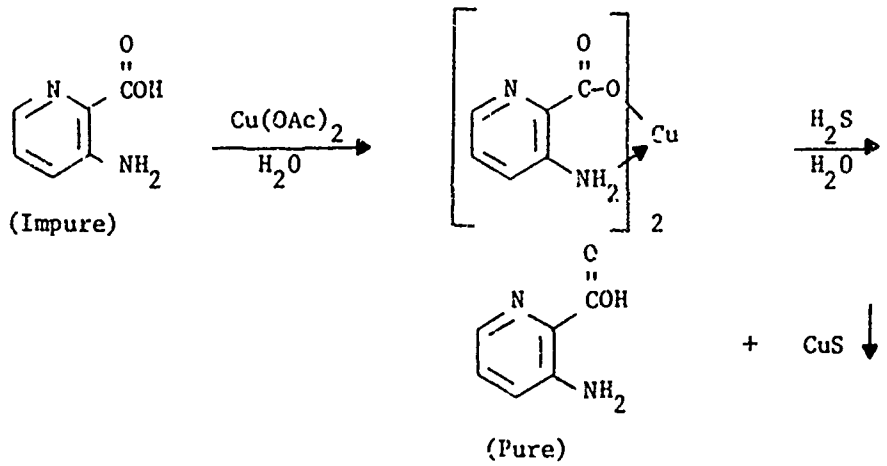
Conventional Route to 2,4-Dichloro-1,5-Naphthyridine



As can be readily seen by inspection of Scheme 4, this route is a multi-step procedure. We have also found that many of the steps involved in Scheme 4 were not amenable to scale-up. Nevertheless, in the initial stages of our research we applied this procedure to prepare the key intermediate in bulk. Also, we deemed it highly necessary to fully characterize the purified intermediates at most steps in order to assure the integrity of the 2,4-dichloro-1,5-naphthyridine. The physical constants and analytical data for all of the intermediates characterized in accord with Scheme 4 are included in Table 11 at the end of this section.

The starting material in Scheme 4 is the commercially available pyridine-2,3-dicarboxylic acid (quinolinic acid). We have started with ca., 2 kg. of this acid for the preparation of the key intermediate in bulk. The preparation of quinolinimide from quinolinic acid was performed as Sucharda has described (25). Purification of the quinolinimide was effected by the improved procedure as reported in the literature (26). When purified via this procedure, the analytical sample (from acetic acid-charcoal, Table 11) melted eleven degrees higher than Sucharda has reported.

The Hoffman degradation of the quinolinimide was performed as Oakes has described (27). This reaction could only be conveniently carried out at the 100g level (of quinolinimide) in the laboratory, and many runs were made. It should be noted that Oakes has reported that 2-aminonicotinic acid is produced as a by-product in this reaction (27). We have never observed this by-product in any of our preparations. In any event, purification of the 3-aminopicolinic acid was effected through the intermediacy of its copper salt.



A sample of the copper salt was washed with hot water, and analytical data for the dried salt are included in Table 11. Presumably, this salt exists in the preferred square planar configuration about the copper atom. The 3-aminopicolinic acid was then liberated from its salt by treatment with hydrogen sulfide. After concentration of the water layer followed by cooling, the 3-aminopicolinic acid separated from solution as a light beige, crystalline solid in low yield. Final purification was effected by recrystallization from water and drying at 110°. Again, it should be noted that the analytically pure acid (Table 11) melted about 10-15° higher than reported in the literature (27,28). The infrared spectrum of the pure, dry acid is reproduced in Figure 38.

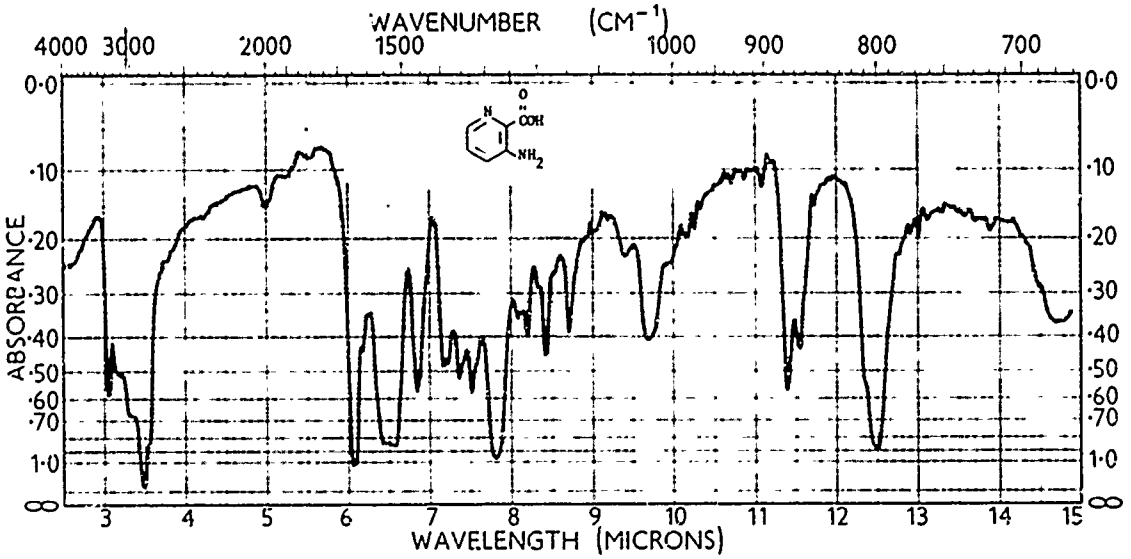
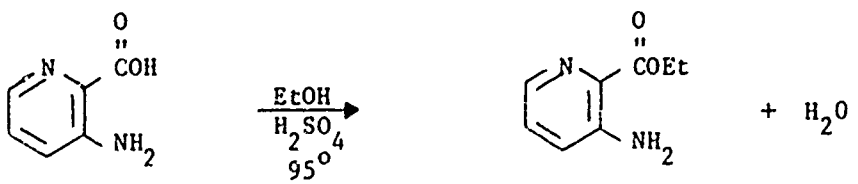


Figure 38. Infrared spectrum of 3-aminopicolinic acid (nujol mull)

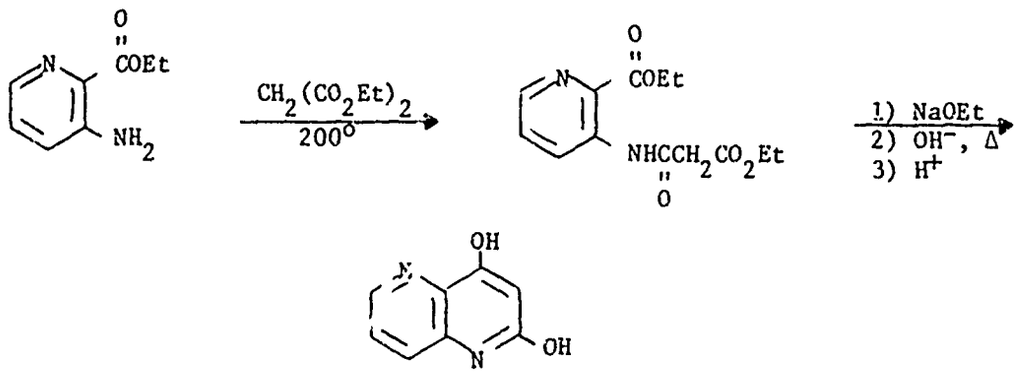
It should be noted that this acid exists as its internal zwitterionic salt, and that only the carboxylate absorption near 6.5μ is observed. Any of the isomeric 2-aminonicotinic (commercially available) would exhibit a carbonyl absorption near 5.8μ. We deemed it highly important to prepare 3-aminopicolinic acid in a very pure state. This is particularly true, since Koller has reported that the isomeric 2-aminonicotinic acid would produce a 1,8-naphthyridine when subjected to the further reaction steps (29). Separation of this 1,8-naphthyridine from the desired 1,5-naphthyridine could prove to be very difficult.

The ethyl ester of 3-aminopicolinic acid was then prepared as Oakes has described using concentrated sulfuric acid as the reaction medium (27).



The pure ester (Table 11)was obtained in 40-50% yield after recrystallization from diethyl ether and exhibited the reported melting point (27,30).

Cyclization of ethyl 3-aminopicolinic acid was then effected according to the von Niementowski method (23).



The intermediate mono-amide was separated from the undesired N,N'-di-(2-ethoxycarbonyl-3-pyridyl) malonamide via their selective solubilities in ether. The Dieckman cyclization of the mono-amide followed by hydrolysis and decarboxylation afforded 2,4-dihydroxy-1,5-naphthyridine as a light yellow powder in ca., 60% yield. This product could be obtained analytically pure (Table 11) only after recrystallization from a large quantity of hot water. The crude material, however, proved to be sufficiently pure for the next step when dried at 110°. The infrared spectrum (Figure 39) is particularly striking and is only in agreement with the almost exclusive existance of this material as its naphthyridone tautomer in the solid state. Other investigators have observed analogous spectra in similar systems (19).

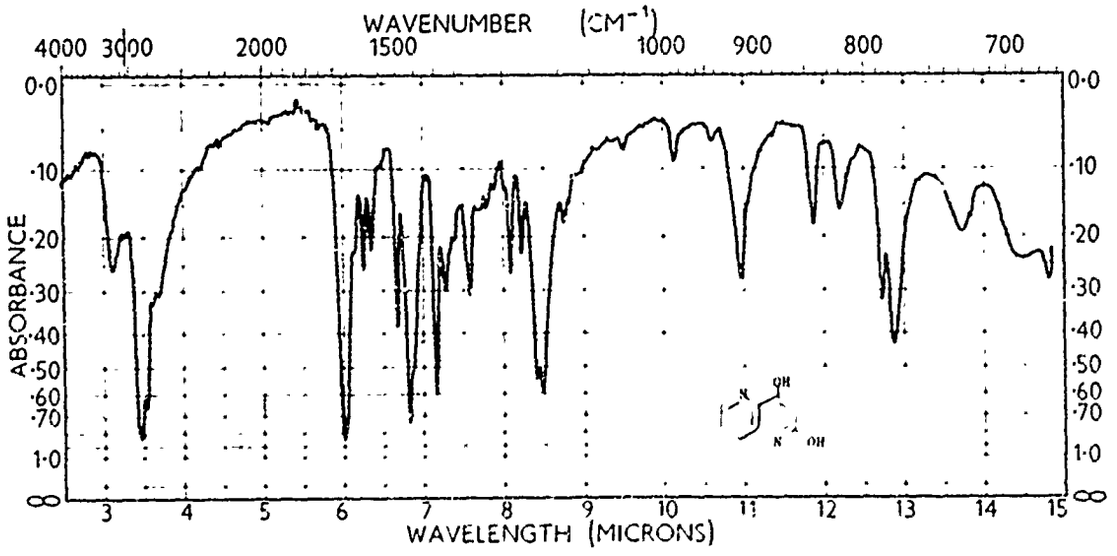
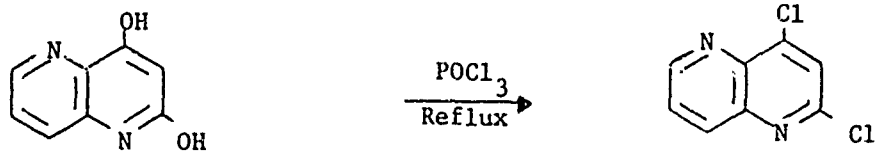


Figure 39. Infrared spectrum of 2,4-dihydroxy-1,5-naphthyridine (nujol mull)

Conversion of 2,4-dihydroxy-1,5-naphthyridine into the corresponding dichloro compound was effected by reaction with hot phosphorus oxychloride.



The yield of crude 2,4-dichloro-1,5-naphthyridine was almost quantitative. Final purification was effected by sublimation, and the analytically pure compound (Table II) was obtained as a sharp melting solid with a heavy, musty odor. The proton spectrum for this derivative is reproduced in Figure 40. The presence of three quartets (doublet of doublets for each of the protons on the B-ring) and the singlet at 2.3τ (the sole proton on the A-ring) is consonant only with a 1,5-naphthyridine structure.

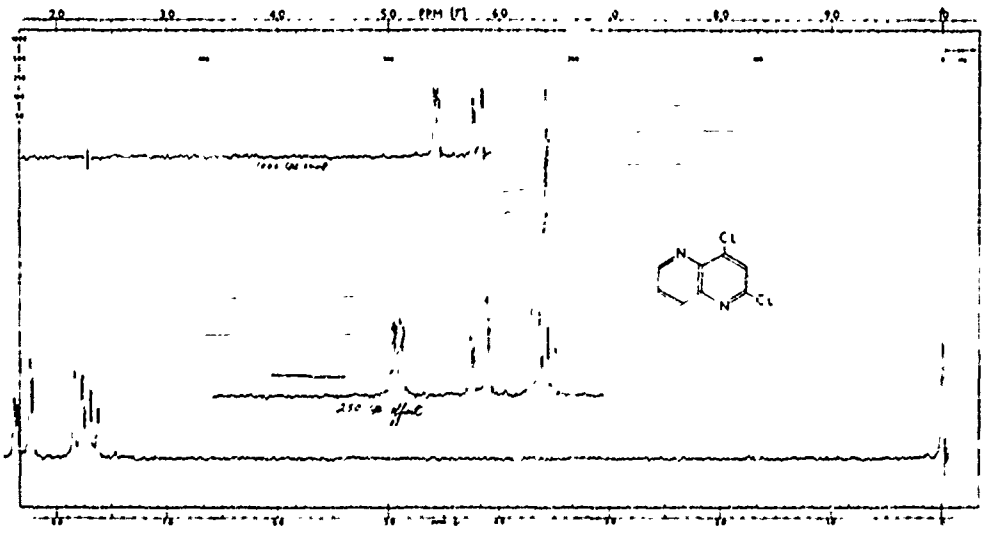
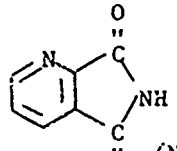
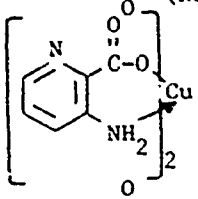
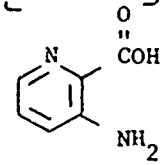
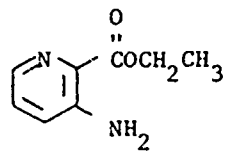
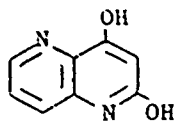
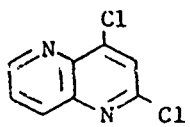


Figure 40. Proton spectrum of 2,4-dichloro-1,5-naphthyridine ($CDCl_3$)

As related earlier, we used the procedure described above to prepare 2,4-dichloro-1,5-naphthyridine in bulk. However, a shorter and much more convenient preparation of this key intermediate is described in the next section.

Table 11

2-Alkoxy-1,5-Naphthyridine Intermediates

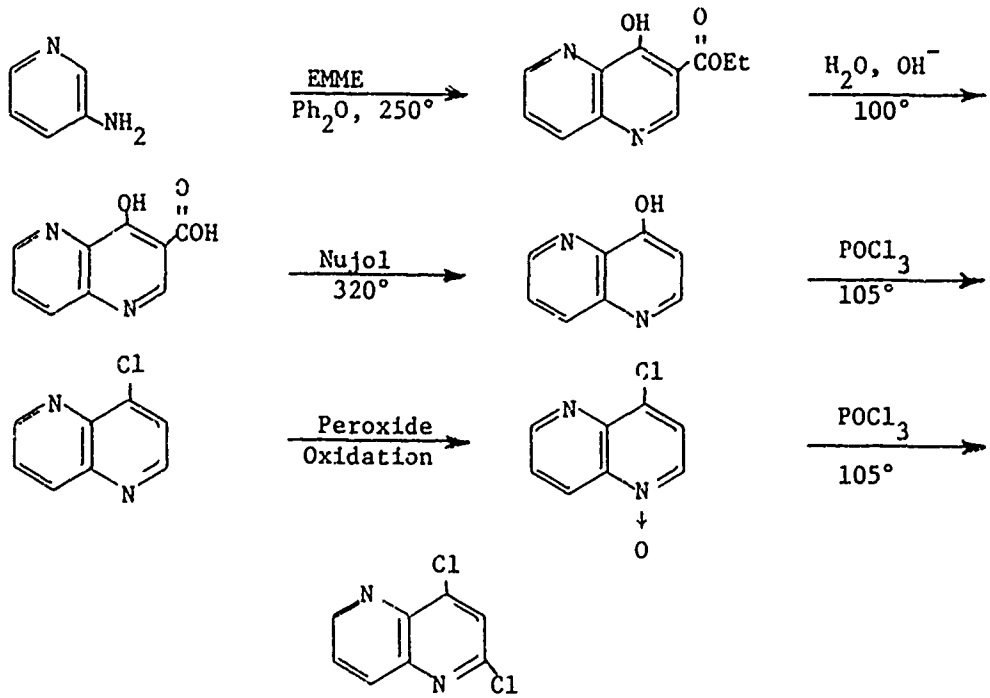
Structure	M.P., °C	Elemental Analysis C	H	N	
 (NP-14)	244-245	56.75 56.64	2.70 2.90	18.92 18.81	Theory Found
 (NP-15)	>300	42.67 42.78	2.98 3.05	16.59 16.59	
 (NP-16)	221-222	52.17 51.77	4.38 4.20	20.29 19.99	
 (NP-17)	131-132	57.82 57.58	6.07 5.97	16.86 16.50	
 (NI-14)	>300	59.25 58.93	3.73 3.88	17.28 17.24	
 (NI-15)	140-141	48.27 47.92	2.02 2.20	14.08 13.80	

Alternative Procedure for the Preparation of 2,4-Dichloro-1,5-Naphthyridine

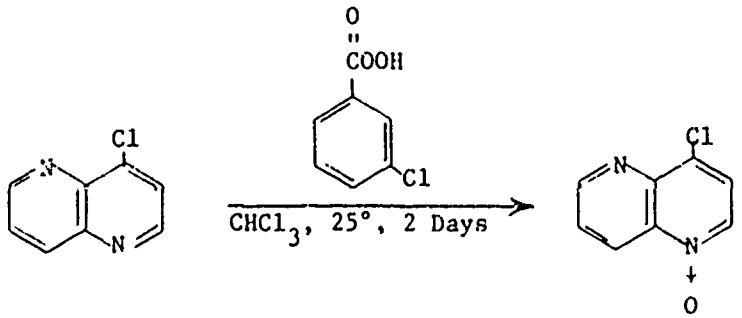
The alternative procedure which may be used for the formation of 2,4-dichloro-1,5-naphthyridine is illustrated by Scheme 5.

Scheme 5

Alterantive Route to
2,4-Dichloro-1,5-Naphthyridine



The first four steps outlined in Scheme 5 have been previously reported by Adams (31). We have noted that purification of the intermediates up to the fourth step is not necessary. In the succeeding step, the peroxide oxidation of the 4-chloro-1,5-naphthyridine, was most conveniently effected utilizing m-chloroperoxybenzoic acid in chloroform solution at room temperature.



The product, 4-chloro-1,5-naphthyridine-1-N-oxide (NI-39), was isolated in 65% yield and exhibited a full elemental analysis (Table 12) which was solely consistent with the mono-N-oxide structure as formulated. The same product was also obtained employing either one or two mole-equivalents of 30% hydrogen peroxide in acetic acid at 40° or 80°. That the ring-1 nitrogen atom has been exclusively oxidized is confirmed by comparison of the proton spectrum of the 4-chloro-1,5-naphthyridine starting material (NI-38, obtained by recrystallization from heptane and sublimation at 80°) with that of the pure N-oxide (Figures 41 and 42, respectively). The H-2 doublet of the 4-chloro-1,5-naphthyridine has shifted upfield upon conversion to the N-oxide. Also, the H-8 doublet of doublets has shifted downfield while the chemical shift of the H-6 proton has remained virtually unchanged.

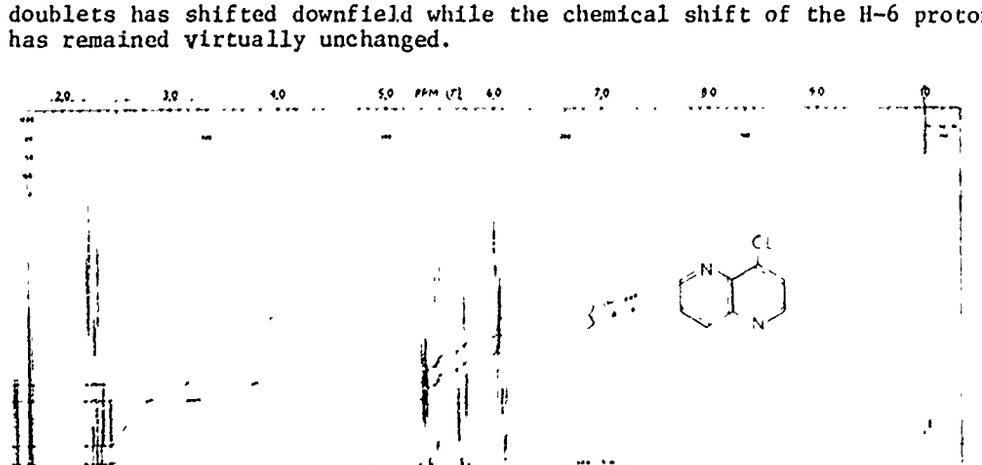


Figure 41. Proton spectrum of 4-chloro-1,5-naphthyridine ($CDCl_3$).

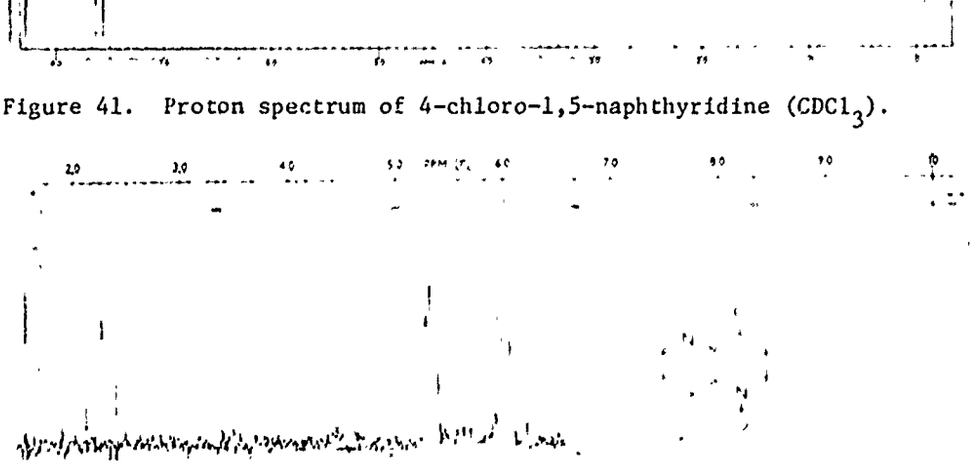
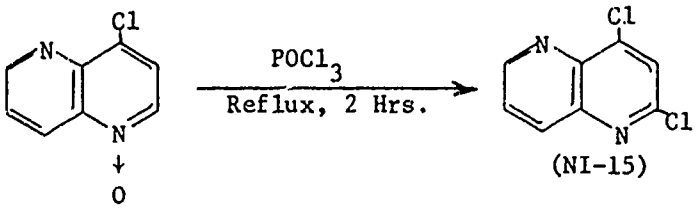


Figure 42. Proto: spectrum of 4-chloro-1,5-naphthyridine-1-N-oxide ($CDCl_3$).

The last step in Scheme 5, the Meisenheimer reaction as applied to the mono-N-oxide, was conducted in refluxing phosphorus oxychloride.

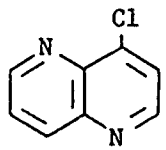
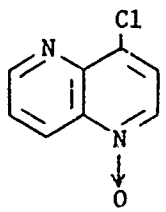


(NI-15)

The dichloro compound was isolated in nearly quantitative yield and exhibited physical and chemical properties idential to authentic 2,4-dichloro-1,5-naphthyridine (NI-15) which we have previously prepared via the lengthy procedure as described in the preceding section. This new synthesis of 2,4-dichloro-1,5-naphthyridine is more amenable to scale-up, and is several steps shorter than the procedure as reported in the literature (23).

Table 12

Precursors to 2,4-Dichloro-1,5-Naphthyridine

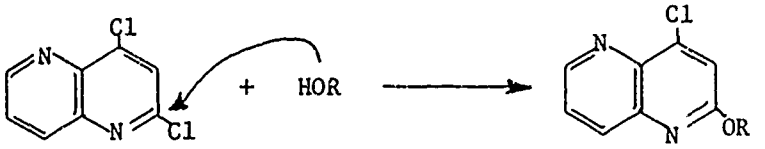
Structure	M.P., °C	Elemental Analysis C	H	N	
 (NI-38)	103-106	58.37 58.37	3.06 3.10	17.02[a] 17.16	Theory Found
 (NI-39)	186-188	53.20 53.16	2.79 2.88	15.51[b] 15.38	

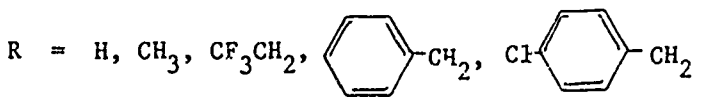
(a) Theory for Cl = 21.54; Found = 21.23
(b) Theory for Cl = 19.63; Found = 20.01

3.2.2 2-Alkoxy-4-Chloro-1,5-Naphthyridine Intermediates

The structures and analytical data of the title derivatives which have been characterized this year are included in Table 13 at the end of this section.

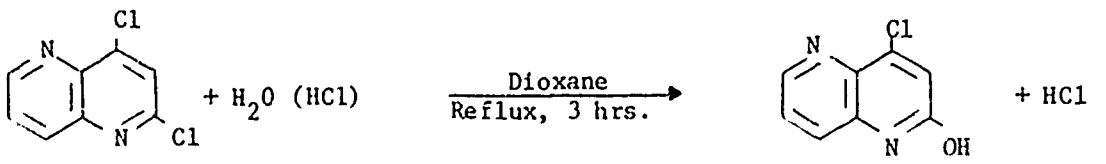
Our prime synthetic approach to the inclusion of alkoxy functionality into the 2-position of the 1,5-naphthyridine ring involved the selective displacement of the 2-chlorine atom from 2,4-dichloro-1,5-naphthyridine (NI-15). In essence, we centered our attention on the conversions shown below:



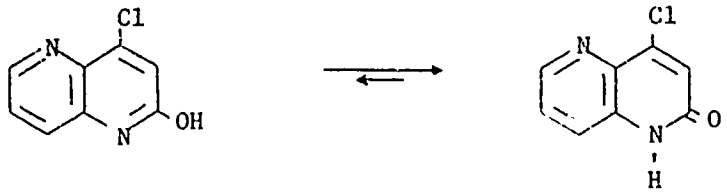


Using an adaptation of the approximate quantum mechanical treatment developed by Longuet-Higgens (32), and subsequently applied to heterocyclic chloro-compounds by Chapman (33), it has been calculated that the 2-position in 2,4-dichloro-1,5-naphthyridine should be the more reactive (23,34). This naphthyridine, therefore, resembles the 2,4-dichloroquinolines rather than the 2,4-dichloroquinazolines. Moreover, this preferential chemical reactivity of the 2-chlorine atom present in 2,4-dichloro-1,5-naphthyridine toward a variety of nucleophiles has been experimentally verified (2,23).

The preparation of 4-chloro-2-hydroxy-1,5-naphthyridine (NI-17) was effected as Oakes and Rydon have described (23). Accordingly, 2,4-dichloro-1,5-naphthyridine was hydrolyzed under acidic conditions in refluxing aqueous dioxane.



The yield of crude product was virtually quantitative. The pure 4-chloro-2-hydroxy-1,5-naphthyridine was obtained as a colorless, microcrystalline solid after recrystallization from ethyl acetate (charcoal). The infrared spectrum for this compound is instructive and is reproduced in Figure 43. The presence of the strong absorption near 6.0μ is consistant solely with the naphthyridone tautomeric structure,



in the solid state. Other investigators have observed analogous spectra in similar systems (19).

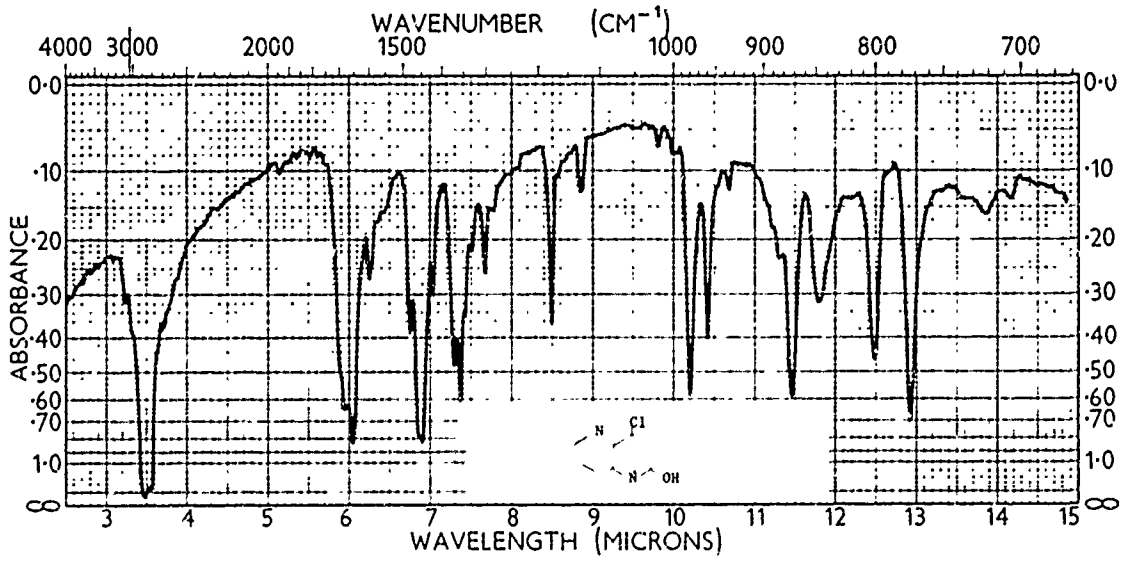
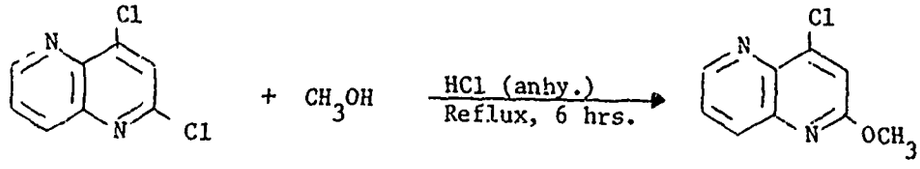


Figure 43. Infrared spectrum of 4-chloro-2-hydroxy-1,5-naphthyridine (nujol mull)

Incorporation of the methoxy group at the 2-position was effected in accord with Cheng's technique (2). Methanol reacted at the more highly activated 2-position of 2,4-dichloro-1,5-naphthyridine under acidic conditions.



The product 4-chloro-2-methoxy-1,5-naphthyridine was isolated in ca. 25% yield from heptane. The proton spectrum (Figure 44) conclusively establishes the methoxy attachment at the 2-position. The resonance for the lone proton on the A ring is present as the high field singlet at 2.8τ. Moreover, the infrared spectrum was devoid of any carbonyl absorptions which would establish the presence of an alkyl group migration from the ether linkage to the nitrogen atom.

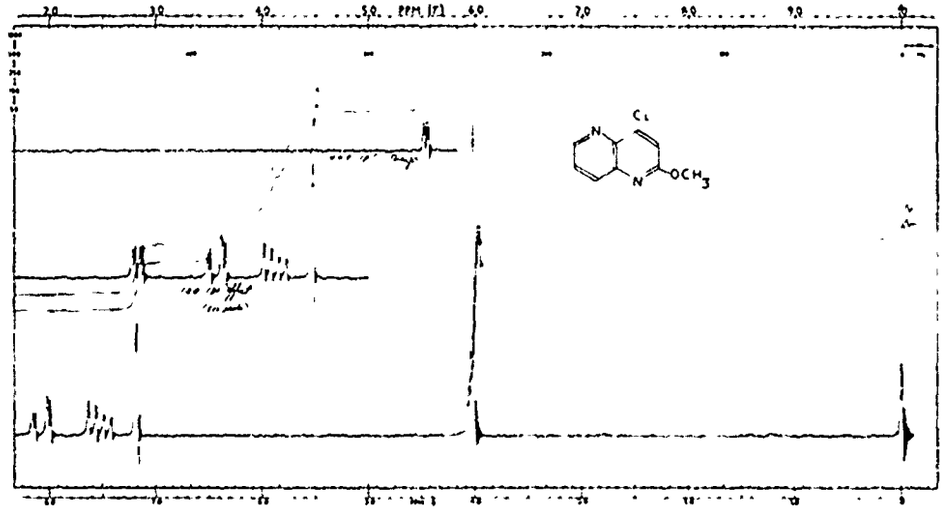
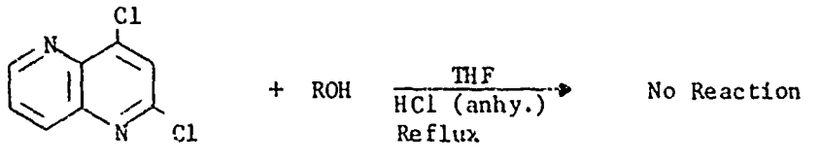


Figure 44. Proton spectrum of 4-chloro-2-methoxy-1,5-naphthyridine ($CDCl_3$)

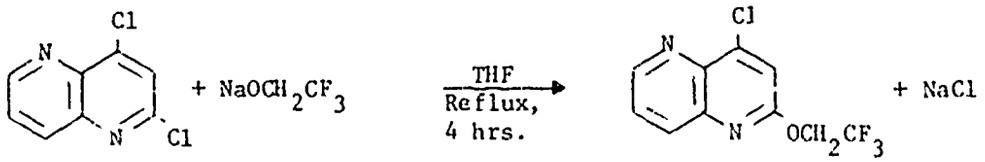
While reaction under acidic conditions worked well for the inclusion of the 2-hydroxy and 2-methoxy functionalities, when this technique was applied to the formation of both 2-(2,2,2-trifluoroethoxy)- and 2-(p-chlorobenzyloxy)-4-chloro-1,5-naphthyridine, no reaction occurred.



$R = CF_3CH_2$, Cl-C$_6$H$_4$-CH_2

Evidently, conversion of the alcohols into the corresponding alkyl chlorides took place before any reaction with the chloro-naphthyridine could occur. In any event, the starting material, 2,4-dichloro-1,5-naphthyridine was completely recovered. Also, no reaction was observed between 2,4-dichloro-1,5-naphthyridine and the pure alcohols under neutral conditions. The results obtained by reaction under basic conditions were more rewarding as explained below.

The sodium alcoholate of 2,2,2-trifluoroethanol was generated in situ in tetrahydrofuran solution at room temperature. This solution was then added into a suspension of 2,4-dichloro-1,5-naphthyridine, and the mixture refluxed for four hours. After filtration of the inorganic salt, crude 4-chloro-2-(2,2,2-trifluoroethoxy)-1,5-naphthyridine (NI-18) was isolated in quantitative yield after removal of solvent.



The analytically pure material (Table 13) was obtained as colorless crystals in 71% yield after recrystallization from hot heptane. The proton spectrum for this intermediate is reproduced in Figure 45. The singlet for the lone proton on the substituted ring is present at 2.92 τ, and the resonance for the three protons on the unsubstituted ring display the typical splitting pattern predicted for an ABC system (doublet of doublets for H-6, H-8 and H-7 at increasing field strength). For comparative purposes, see the isomeric retroisomer, 4-chloro-6-(2,2,2-trifluoroethoxy)-1,5-naphthyridine (Figure 15).

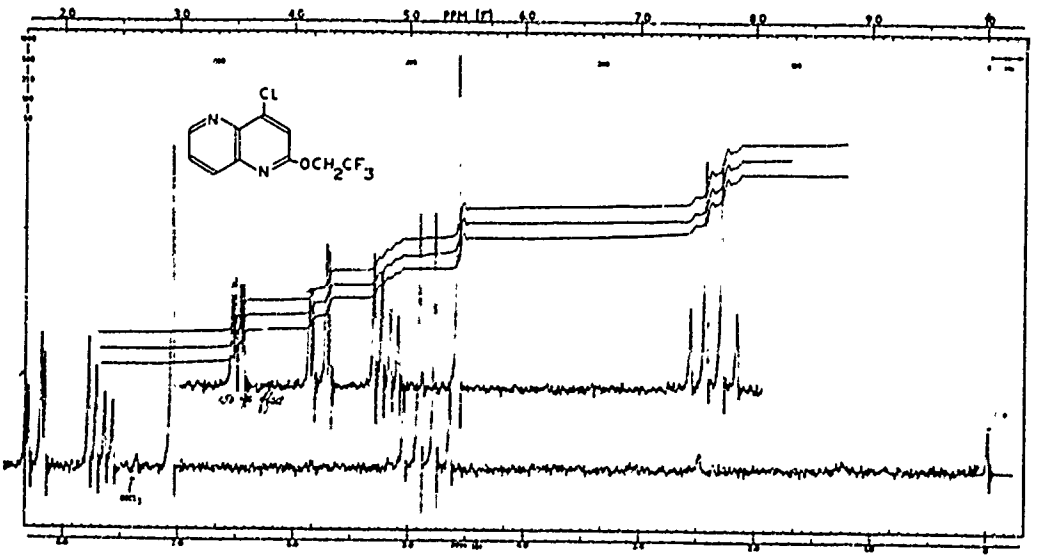


Figure 45. Proton spectrum of 4-chloro-2-(2,2,2-trifluoroethoxy)-1,5-naphthyridine ($CDCl_3$).

The preparation of 2-benzyloxy-4-chloro-1,5-naphthyridine was performed by reaction of the sodium salt of benzyl alcohol with 2,4-dichloro-1,5-naphthyridine in refluxing tetrahydrofuran.

The product, NI-40, was isolated in 35% yield as described in the experimental section. Its proton spectrum (Figure 46) is consistent with the formulated structure.

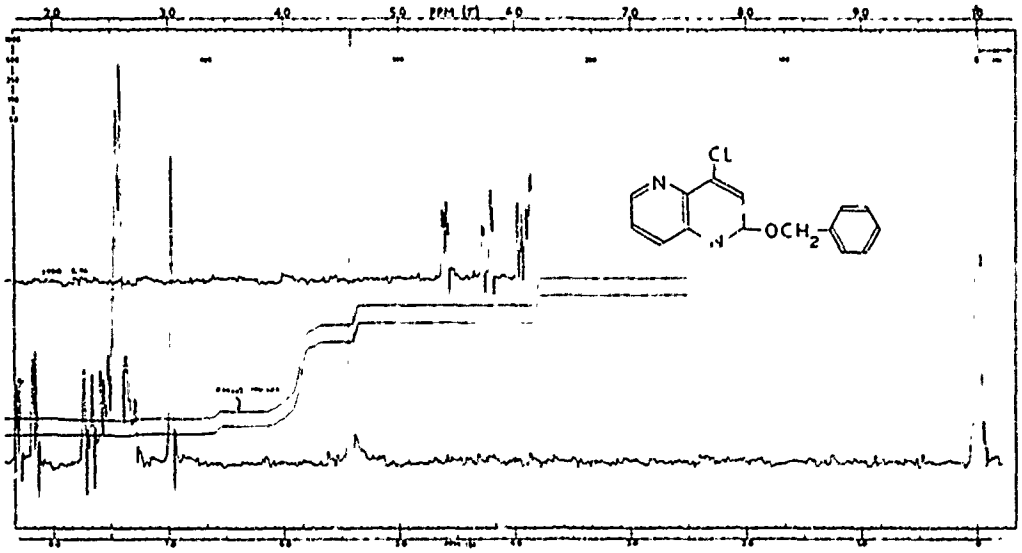
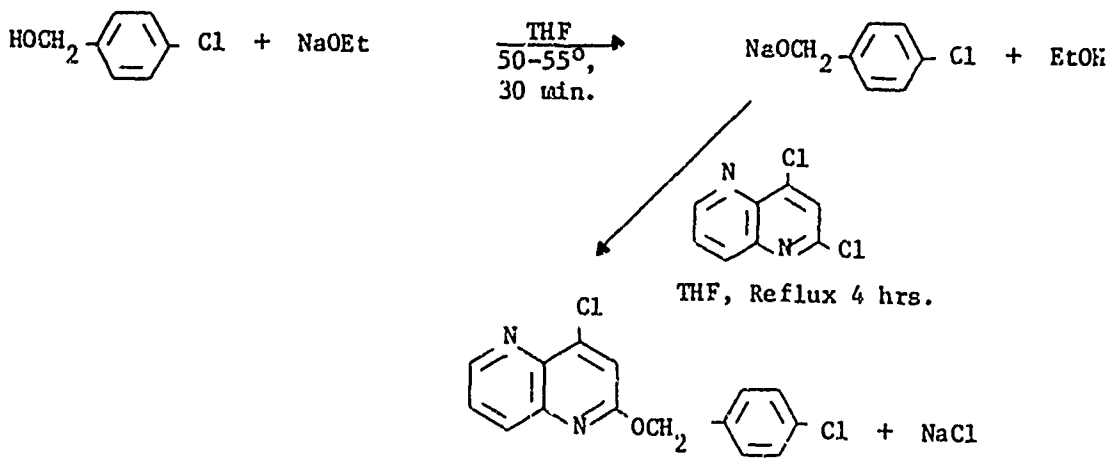


Figure 46. Proton spectrum of 2-benzyloxy-4-chloro-1,5-naphthyridine ($CDCl_3$)

The preparation of 4-chloro-2-(p-chlorobenzyloxy)-1,5-naphthyridine (NI-19) was effected via an analogous procedure. We used our previously successful metathetical procedure to generate the sodium salt of p-chlorobenzyl alcohol under moderate conditions. Next, 2,4-dichloro-1,5-naphthyridine was added and the mixture refluxed for four hours.



After filtration and removal of solvent, NI-19 was obtained in low yield (16%) only after careful fractional recrystallization from hot heptane to remove unreacted starting materials. The proton spectrum for the analytically pure product (Table 13) is reproduced in Figure 47 and is clearly in accord with the formulated structure. The aromatic protons of the p-chlorobenzyloxy ring are present as a sharp singlet at 2.58τ, and the methylene ($-OCH_2-$) protons are present as a sharp singlet at 4.60τ in the correct intensity ratio.

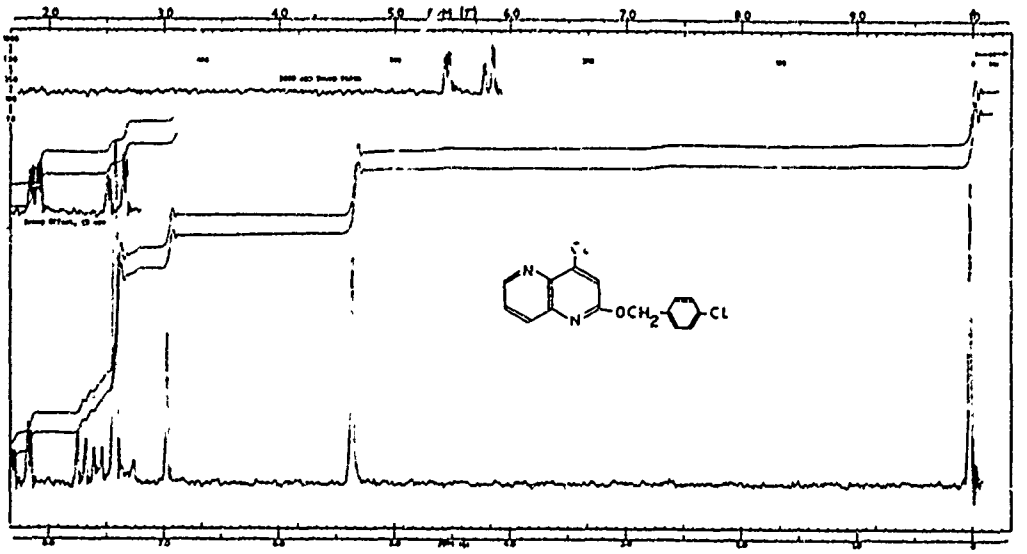


Figure 47. Proton spectrum of 4-chloro-2-(p-chlorobenzyloxy)-1,5-naphthyridine ($CDCl_3$).

Table 13

2-Alkoxy-4-Chloro-1,5-Naphthyridine Intermediates

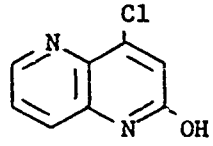
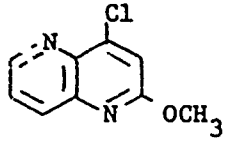
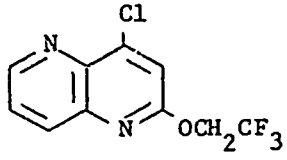
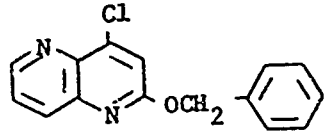
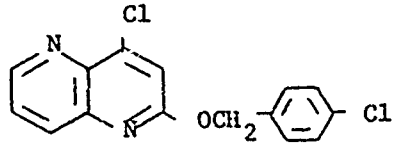
Structure	M.P., °C	Elemental Analysis C	H	N	
 (NI-17)	268.0-268.5	53.20 53.01	2.79 2.90	15.51 15.24	Theory Found
 (NI-16)	112-113	55.54 55.72	3.63 3.79	14.40[a] 14.44	
 (NI-18)	153.0-153.5	45.73 45.84	2.30 2.41	10.67[b] 10.86	

Table 13 (Cont'd.)

Structure	M.P., °C	Elemental Analysis C	H	N
 (NI-40)	139-140	66.54 66.49	4.10 4.10	10.35(c) 10.43
 (NI-19)	137-138	59.03 59.28	3.30 3.34	9.18(d) 9.17

(a) Theory for Cl = 18.22; Found = 18.37.

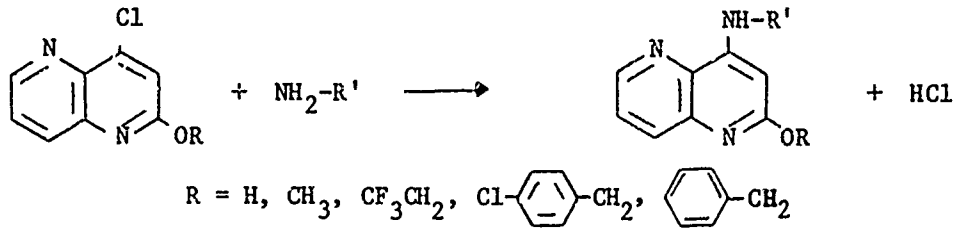
(b) Theory for Cl = 13.50; Found 13.50.

(c) Theory for Cl = 13.10; Found = 12.78.

(d) Theory for Cl = 23.24; Found = 22.98.

3.2.3 Formation of the 2-Alkoxy-4-Amino-1,5-Naphthyridines

As disclosed in Scheme 3 in the introduction to this section, the final step in the synthesis of the target 2-alkoxy-4-amino-1,5-naphthyridines involves the displacement of chlorine from the intermediates discussed in the preceding section by diamines.



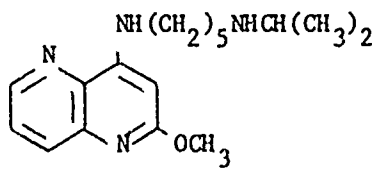
R' = Pamaquine, Pentaquine and Primaquine side chains.

Immediately below, we have first described the target derivatives which were prepared this year in accord with this technique. Subsequently, we have described a complicating factor in this synthesis, the formation of several 2,4-diamino-1,5-naphthyridine intermediates. The latter products were obtained by reaction of the diamines with the 4-chloro-2-alkoxy-1,5-naphthyridines which bear electron withdrawing groups in the 2-position.

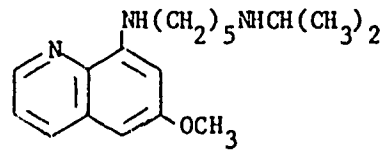
Naphthyridine Targets

The physical constants and analytical data for the 2-alkoxy-4-amino-1,5-naphthyridines which were characterized this year are included in Table 14 at the end of this section.

Utilizing the procedure described above, this year we have prepared and characterized 2-methoxy-4-(5-isopropylaminopentylamino)-1,5-naphthyridine ("5-Azapentaquine", NT-4) both as the free base and β-resorcylate salt. The structural similarity of NT-4 to pentaquine is readily apparent (see below). Indeed, this compound is the 1,5-naphthyridine isostere of the 8-aminoquinoline, pentaquine.

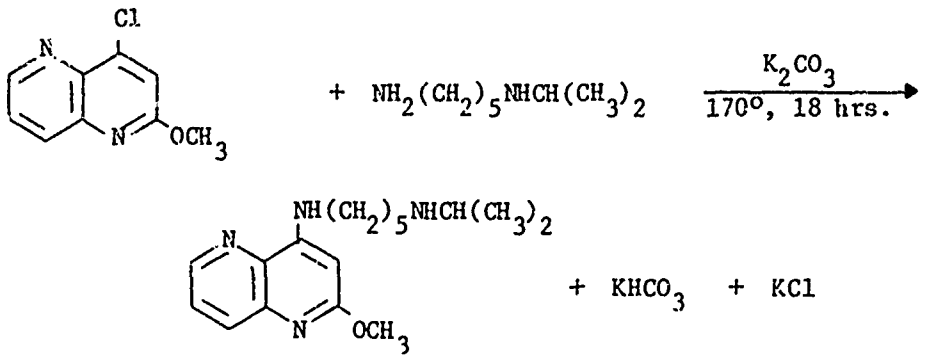


(NT-4)



(Pentaquine)

The details of its preparation are as follows. The direct reaction between 4-chloro-2-methoxy-1,5-naphthyridine and excess 5-isopropylaminopentylamine (13) at 170° led to the preparation of a mixture of products. The presence of carbonyl peaks near 6.0μ in the crude mixture provided clear evidence that methyl migration from the ether linkage to the adjacent nitrogen atom was occurring under these conditions. As Cheng has pointed out for a similar system, the hydrochloric acid produced in this reaction probably catalyzes the alkyl group migration (2,35). The reaction was therefore conducted in the presence of one mole-equivalent of the acid scavenger, potassium carbonate.



After filtration of the inorganic salts, the crude reaction mixture was partitioned between ether and dilute aqueous sodium hydroxide. The ether layer was then dried and solvent removed to afford a brownish liquid. Analytically pure (Table 14) 2-methoxy-4-(5-isopropylaminopentylamino)-1,5-naphthyridine, NT-4, was then isolated as a yellow-orange liquid by a slow, controlled molecular distillation. The proton spectrum for 5-Azapentaquine is reproduced in Figure 48. The occurance of a single doublet for the isopropyl group at 9.0μ, coupled with the appearance of a clean triplet for the 4-amino proton at 3.48τ conclusively proves that reaction has occurred exclusively at the primary amino group of 5-isopropylaminopentylamine. As discussed in detail previously, presumably the greater steric requirements necessary for reaction at the secondary amino group of this diamine leads to exclusive attack by the primary amine function. This is in agreement with Tarbell's supposition (not conclusively proven) that only the primary amino group of 3-isopropylaminopropylamine reacted at the 4-position present in 4,7-dichloroquinoline (14).

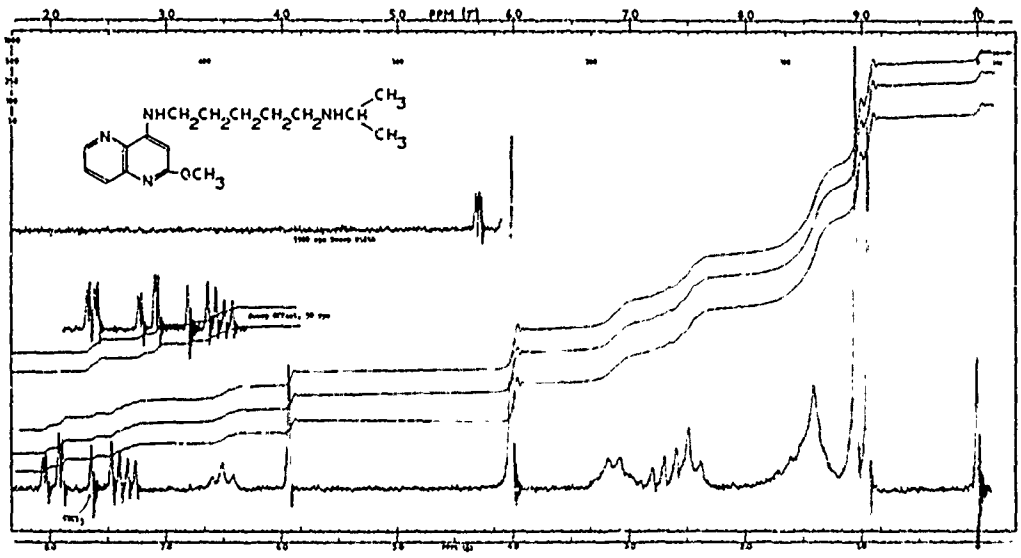
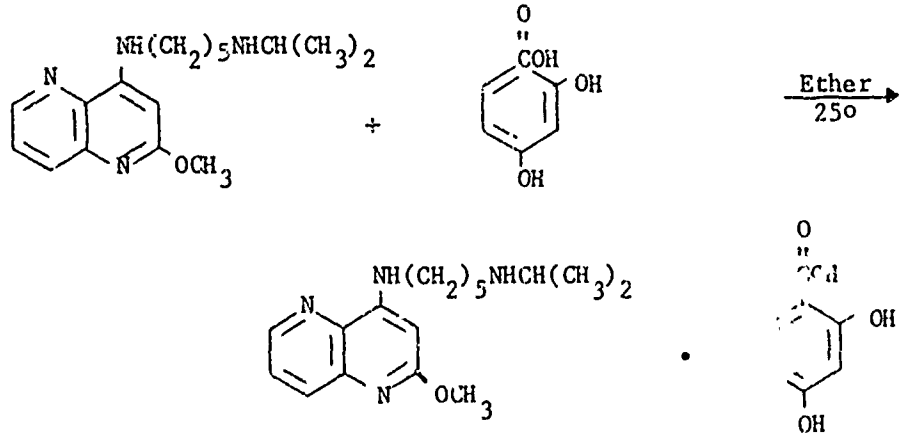


Figure 48. Proton spectrum of 2-methoxy-4-(5-isopropylaminopentylamino)-1,5-naphthyridine ($CDCl_3$).

As disclosed previously in this report, we have had considerable difficulty isolating characterizable salts of these 4-amino-1,5-naphthyridines. The hydrochlorides, sulfates, phosphates and citrates have proven to be highly hygroscopic or deliquescent materials. Isolable picrates could be prepared, however, the well-known toxicity of picric acid salts obviates their testing as candidate drugs. We have had greater success in preparing well characterizable β-resorcylates which contain a biologically acceptable gegen-ion (15). Accordingly, the β-resorcylate salt of 2-methoxy-4-(5-isopropylaminopentylamino)-1,5-naphthyridine was prepared by the slow addition of an ether solution of β-resorcylic acid to the free base in ether solution.



The precipitated salt was then simply isolated by filtration. It should be noted that the filtrations had to be conducted under a nitrogen atmosphere since the salt was mildly hygroscopic under work-up. After drying, however, the salt did not exhibit any deliquescent properties. The analytical data for the precipitated salt (Table 14)revealed the presence of a single β-resorcylate anion. The same analysis was obtained even when an excess of the acid was used. The infrared spectrum for this derivative is reproduced in Figure 49.

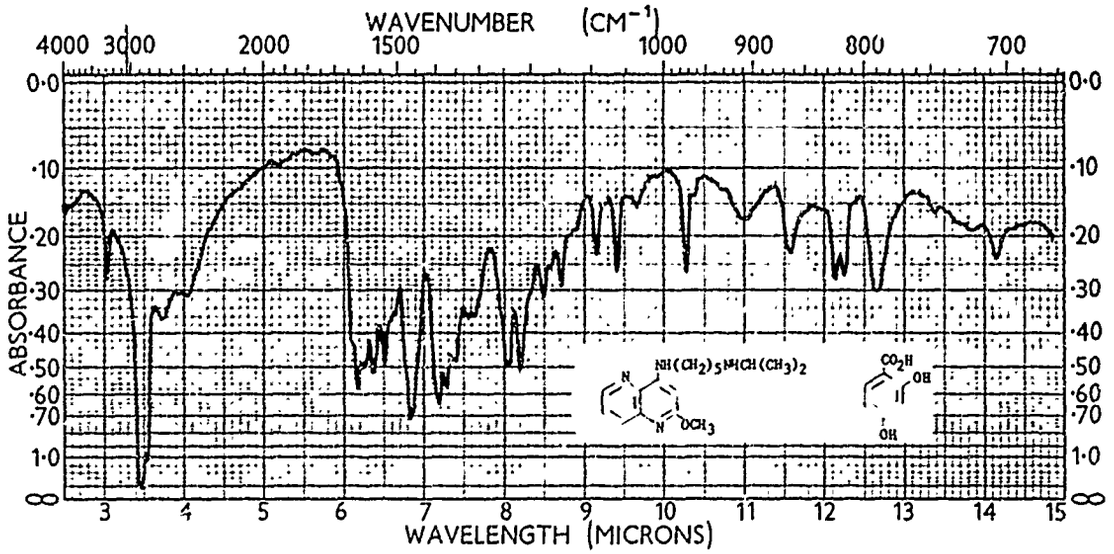
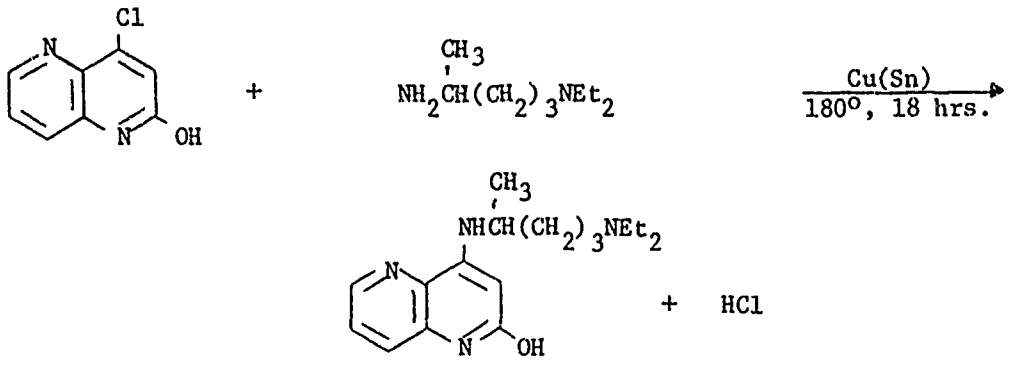
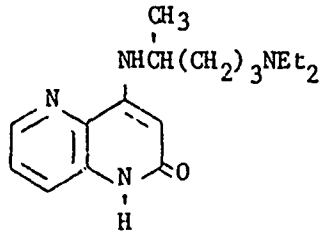


Figure 49. Infrared spectrum of 2-methoxy-4-(5-isopropylaminopentylamino)-1,5-naphthyridine β-resorcylate (nujol mull).

The reactions of 4-chloro-2-hydroxy-1,5-naphthyridine (NI-17) with diamines were also investigated this year. While the 4-chlorine atom present in this precursor has been reported to be particularly unreactive with regard to displacement with aromatic amines (23), we have found to the contrary that NI-17 reacted well with both 2-amino-5-diethylaminopentane and 5-isopropylaminopentylamine. We first elected to react NI-17 with 2-amino-5-diethylaminopentane (novaldiamine) as a route to the pamaquine side chain analog. Experimentally, 4-chloro-2-hydroxy-1,5-naphthyridine was reacted with excess novaldiamine in the presence of a catalytic quantity of copper-bronze for eighteen hours at 180°.



After the usual work-up procedure, 2-hydroxy-4-(4-diethylamino-1-methylbutylamino)-1,5-naphthyridine (NT-6) was isolated as a high boiling gum which quickly solidified after purification by molecular distillation. The analytical sample (Table 14) was obtained as a white solid (m.p., 95-96°) after recrystallization from ether (charcoal)-pentane. The infrared spectrum for this derivative is reproduced in Figure 50. The strong absorption near 6.1μ clearly indicates that this material exists as its naphthyridone tautomer,



in the solid state. This spectrum should be compared with that of the starting material, 4-chloro-2-hydroxy-1,5-naphthyridine (Figure 43). Also, the proton spectrum, Figure 51, is in complete accord with the structure as formulated. The strong upfield shift of the H-3 singlet (4.22τ) upon substitution of an amino group for a chlorine atom is readily apparent.

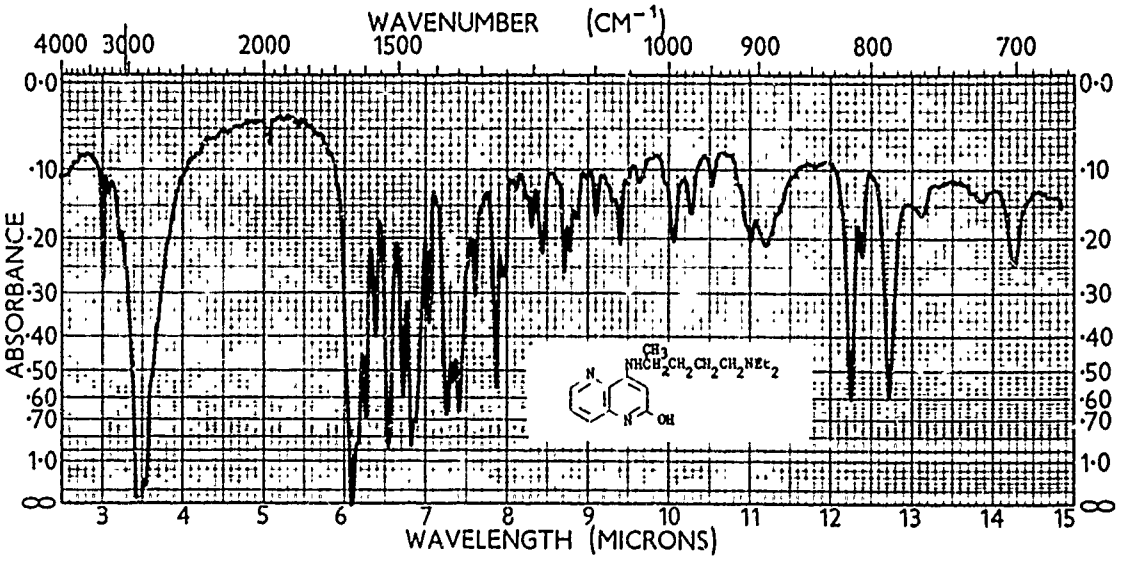


Figure 50. Infrared spectrum of 2-hydroxy-4-(4-diethylamino-1-methylbutylamino)-1,5-naphthyridine (nujol mull).

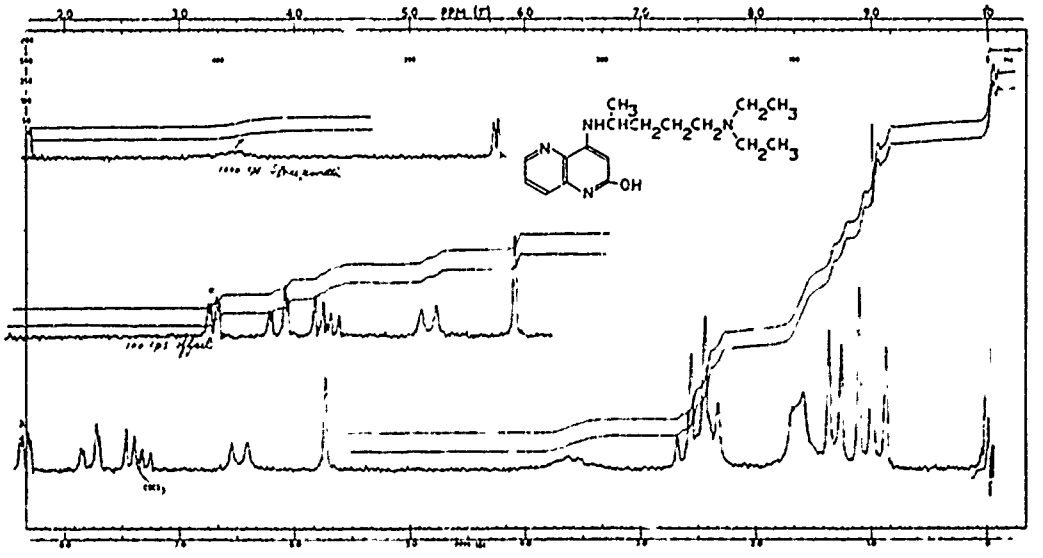
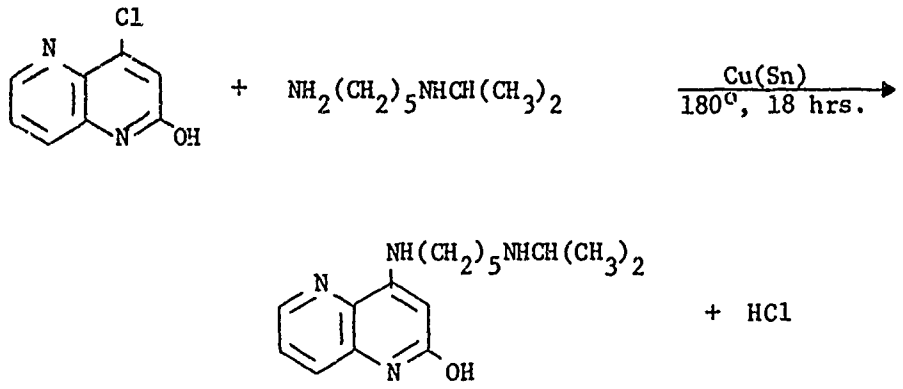


Figure 51. Proton spectrum of 2-hydroxy-4-(4-diethylamino-1-methylbutylamino)-1,5-naphthyridine ($CDCl_3$).

The inclusion of the pentaquine side chain cnto 2-hydroxy-4-amino-1,5-naphthyridine has also been effected via essentially the same procedure.



In this instance, the isolation of the product, 2-hydroxy-4-(5-isopropylaminopentylamino)-1,5-naphthyridine (NT-7), was much simpler. After neutralization of the reaction mixture with aqueous base, the addition of ether to the two phase system immediately precipitated NT-7 as an off white solid. After recrystallization from tetrahydrofuran (charcoal)-ether; the analytical sample was obtained as a white solid. The proton spectrum, Figure 52, revealed a clean doublet for the isopropyl methyl groups at 8.98τ in addition to a broad triplet for the ring amino proton (3.42τ). There is, therefore, little doubt that the pentaquine side-chain is attached as formulated.

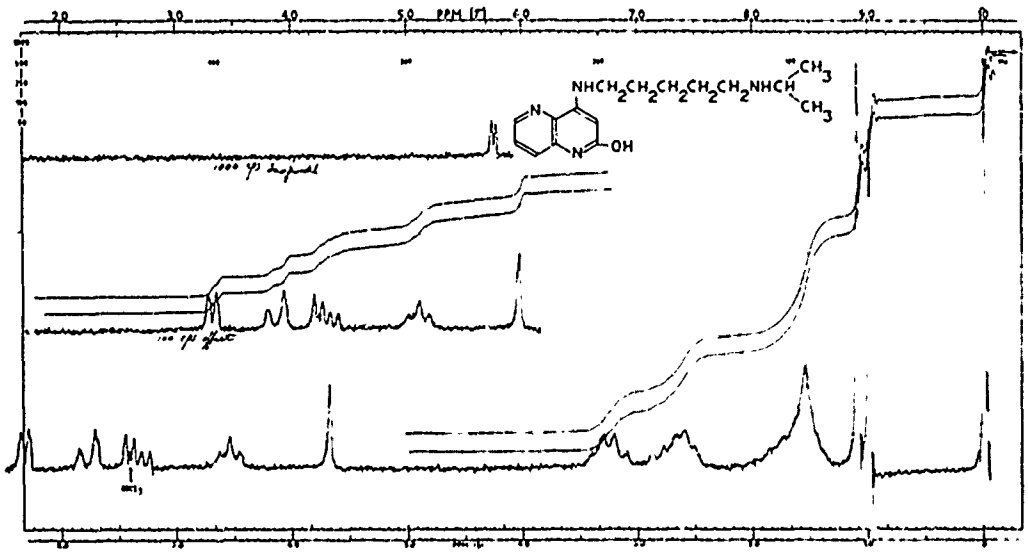
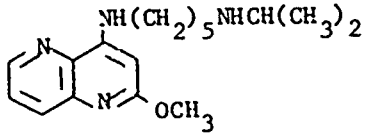
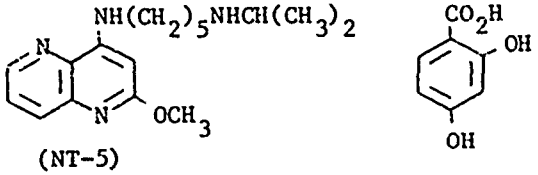
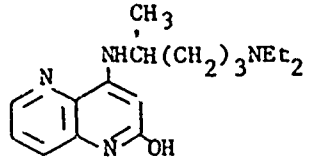
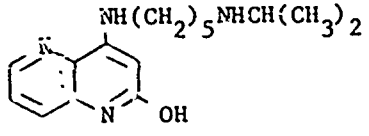


Figure 52. Proton spectrum of 2-hydroxy-4-(5-isopropylaminopentylamino)-1,5-naphthyridine ($CDCl_3$).

Table 14

2-Alkoxy-4-Amino-1,5-Naphthyridines

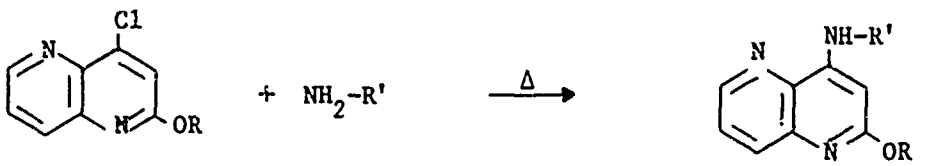
Structure	M.P., °C B.P., °C(mm)	Elemental Analysis C	 H	 N	
 (NT-4)	160-170 (0.04)(a)	67.51 67.73	8.67 8.78	18.53 18.05	Theory Found
 (NT-5)	167-168	63.14 62.73	7.07 7.13	12.27 11.76	
 (NT-5)	95-96	67.51 67.34	8.67 8.72	18.53 18.35	
 (NT-7)	117-118(b)	66.63 66.19	8.39 8.49	19.43 18.94	

(a) Molecular distillation.

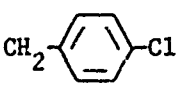
(b) Sharp surface wetting at 87.0-87.5°.

2,4-Diamino-1,5-Naphthyridines

As disclosed in the preceding section, we have prepared several of the target 2-alkoxy-4-amino-1,5-naphthyridines by the interaction of diamines with our preformed 2-alkoxy-4-chloro-1,5-naphthyridines. We have also attempted to expand upon the derivatives of this class by employing our previously characterized 2-(2,2,2-trifluoroethoxy)- and 2-(p-chlorobenzyloxy)-4-chloro-1,5-naphthyridines (NI-18 and NI-19).



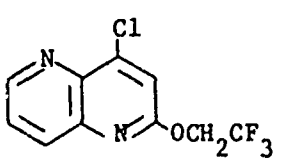
R = CH_2CF_3, R' = $(CH_2)_5NHCH(CH_3)_2$,



$CH(CH_2)_3NEt_2$
|
CH_3

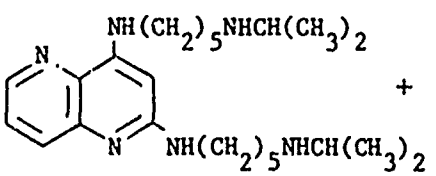
The reactions as performed to date, however, clearly disclose that both the 4-chlorine atom, and the 2-alkoxy group are displaced by the excess of diamine present at the elevated temperatures. Evidently, the 2-alkoxy bond in NI-18 and NI-19 is weakened with respect to displacement reactions by the presence of strongly electron withdrawing groups. We are presently attempting these reactions at both lower temperatures and in the presence of only one mole-equivalent of diamines in an effort to circumvent this difficulty. In any event, the results attained to date are explained in detail below.

The reaction of 2-(2,2,2-trifluoroethoxy)-4-chloro-1,5-naphthyridine (NI-18) with 5-isopropylaminopentylamine was conducted via our standard technique. Upon work-up of the reaction mixture, however, the sole isolable product proved to be 2,4-di-(5-isopropylaminopentylamino)-1,5-naphthyridine (NI-30).



+ $NH_2(CH_2)_5NHCH(CH_3)_2$ (excess)

$\xrightarrow[170°,\ 18\ hrs.]{K_2CO_3}$



+ HCl + CF_3CH_2OH

This product was isolated as a viscous oil in 67% yield by molecular distillation. The data upon which we have based the formulated structure include both full elemental analyses (Table 15) and its proton spectrum (Figure 53). That the trifluoroethoxy group has been lost in this product is immediately apparent by the conspicuous absence of a quartet near 5.5τ in the proton spectrum. In addition, two broad triplets are observed near 3.6 and 4.5τ which can only be attributed to the structure as formulated. The low field triplet (3.60τ) can be unambiguously assigned to the 4-amino proton of the pentaquine side-chain by analogy to the spectra of our previously characterized 2-alkoxy-4-amino-1,5-naphthyridines. The remaining broad triplet at 4.50τ is therefore attributable to the amino proton of the pentaquine side chain which has been introduced into the 2-position.

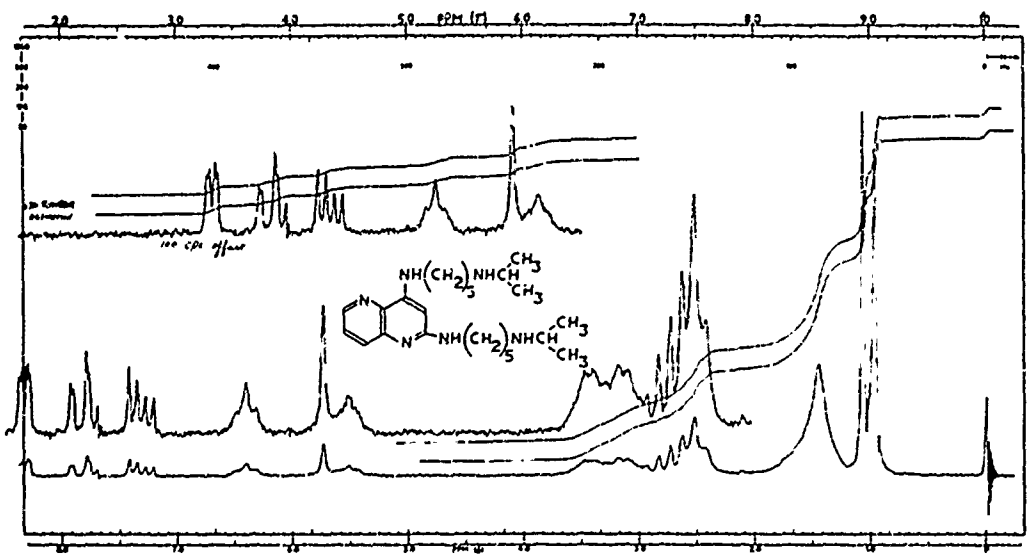
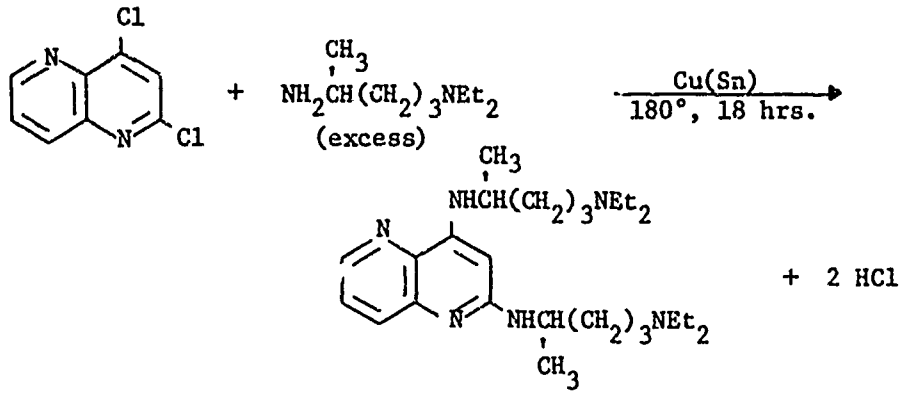


Figure 53. Proton spectrum of 2,4-di-(5-isopropylaminopentylamino)-1,5-naphthyridine ($CDCl_3$).

The corresponding reaction of 2-(p-chlorobenzyloxy)-4-chloro-1,5-naphthyridine (NI-19) with 5-isopropylaminopentylamine as conducted on a test scale also revealed the loss of the 2-alkoxy substituent. Analogous results were observed when NI-18 and NI-19 were reacted with an excess of 2-amino-5-diethylaminopentane at elevated temperatures in an effort to introduce the pamaquine side chain into the 4-position. Examination of the proton spectra of the crude products again revealed the loss of the 2-alkoxy substituents. In both of these cases, however, no pure component could be isolated by molecular distillation. We therefore prepared the expected product, 2,4-di(4-diethylamino-1-methylbutylamino)-1,5-naphthyridine, via an unambiguous route for comparative purposes. Our previously characterized 2,4-dichloro-1,5-naphthyridine (NI-15) was reacted with 2-amino-5-diethylaminopentane via our standard procedure.



The reaction proceeded well as indicated, and analytically pure 2,4-di-(4-diethylamino-1-methylbutylamino)-1,5-naphthyridine (NI-32) was isolated in ca., 60% yield by molecular distillation. The proton spectrum is reproduced in Figure 54, and exhibits the predicted broad doublets at 3.70τ and 4.80τ for the 4- and 2-amino protons respectively. Comparison of this spectrum with the crude products from the reactions of NI-18 and NI-19 with 2-amino-5-diethylaminopentane did indeed reveal that NI-32 was present in the mixture.

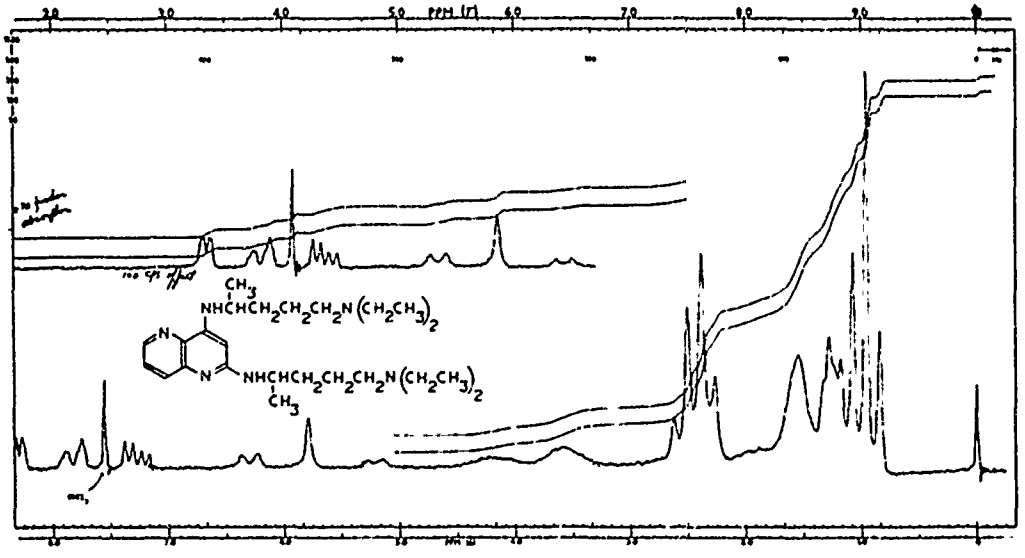
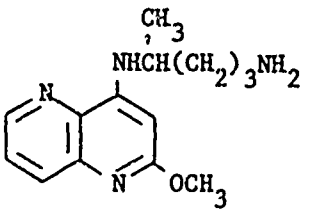


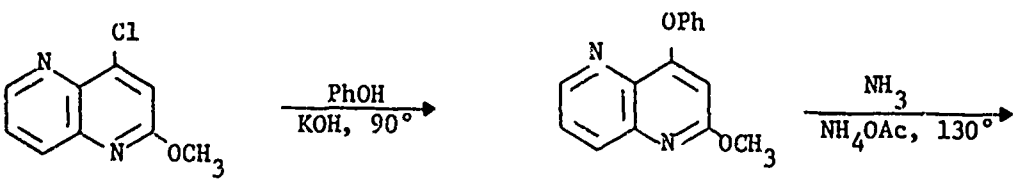
Figure 54. Proton spectrum of 2,4-di-(4-diethylamino-1-methylbutylamino)-1,5-naphthyridine ($CDCl_3$).

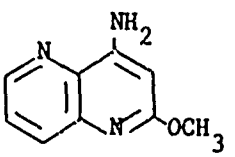
The β-resorcylate salts of both of these 2,4-diamino-1,5-naphthyridines were prepared by the addition of an excess of 2,4-dihydroxybenzoic acid into ether solutions of the analytically pure free bases (NI-30 and NI-32) in ether at room temperature. The products immediately separated from solution, and the empirical formulae assigned to the resultant salts (NI-31 and NI-33) are based upon the analytical data reported in Table 15. Duplicate analyses performed on both the same, and repetitive preparations, revealed identical values and are only in agreement with the structures as formulated.

In a second general area, we currently involved with the introduction of the primaquine side chain into these 2-alkoxy-4-amino-1,5-naphthyridines. As our first candidate, we are attempting the preparation of the following naphthyridine isostere (5-aza analog) of primaquine itself.



Our synthetic approach to these primaquine side chain analogs essentially follows the reported literature technique as discussed previously in this report (16). Requisite in this approach is the synthesis of 4-amino-2-methoxy-1,5-naphthyridine. Our first approach to the synthesis of this intermediate was patterned after Goldberg's synthesis of a related 4-amino-1,5-naphthyridine (5).





As delineated in the experimental section, preformed 4-chloro-2-methoxy-1,5-naphthyridine (NI-16) was first reacted with phenol under basic conditions. Reaction of the crude phenoxy intermediate with ammonia was then conducted in molten ammonium acetate at 130°. Upon work-up of the reaction mixture, however, it was evident that the second step did not proceed, since the unreacted intermediate (2-methoxy-4-phenoxy-1,5-naphthyridine, NI-34) was the sole isolable product. This phenoxy intermediate,

NI-34, was isolated as a white solid after recrystallization from ether-pentane. The infrared spectrum is reproduced in Figure 55 and clearly exhibits a strong phenoxy absorption near 8.3 μ.

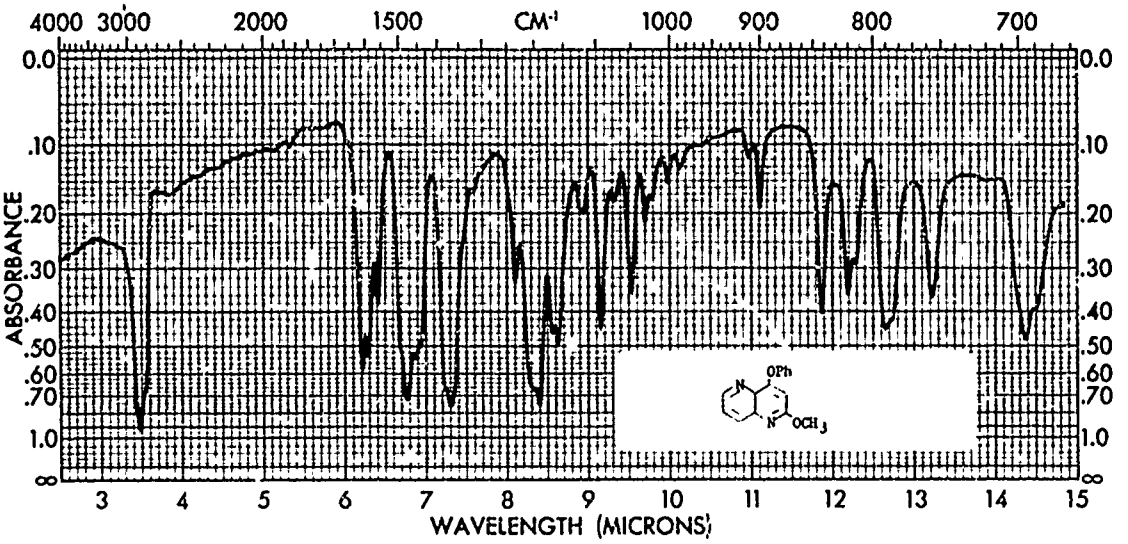
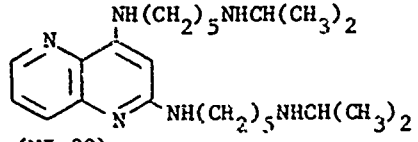
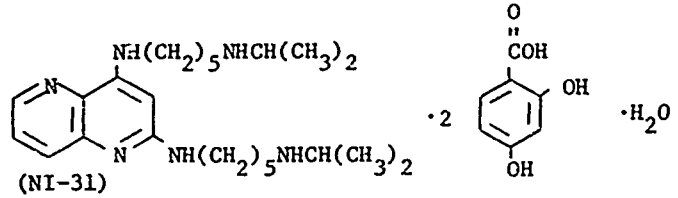
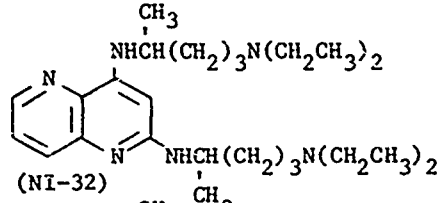
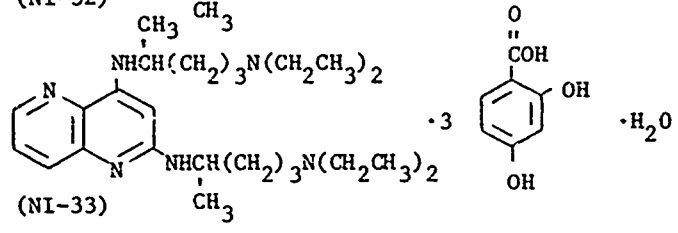
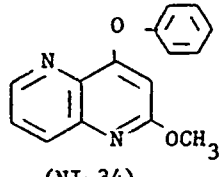


Figure 55. Infrared spectrum of 2-methoxy-4-phenoxy-1,5-naphthyridine (nujol mull).

Present plans call for the introduction of the 4-amino group utilizing ethanolic-ammonia under high pressure.

Table 15

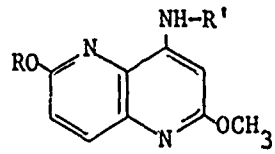
2-Alkoxy-1,5-Naphthyridine Intermediates

Structure	B.P., °C (mm) M.P., °C	Elemental Analysis C	H	N	
 (NI-30)	190-195(0.04) (a)	69.52 69.46	10.21 10.31	20.27 20.34	Theory Found
 (NI-31)	106-109	61.60 61.55	7.62 7.41	11.34 11.15	
 (NI-32)	190-195(0.04) (a)	70.54 70.61	10.47 10.53	18.99 18.99	
 (NI-33)	108-111	61.15 61.01	7.21 6.98	9.10 9.22	
 (NI-34)	72-73	71.41 71.60	4.80 4.88	11.11 11.30	

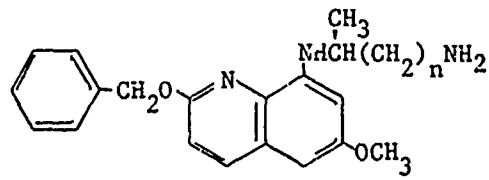
(a) Molecular distillation

3.3 2,6-Dialkoxy-4-Amino-1,5-Naphthyridines

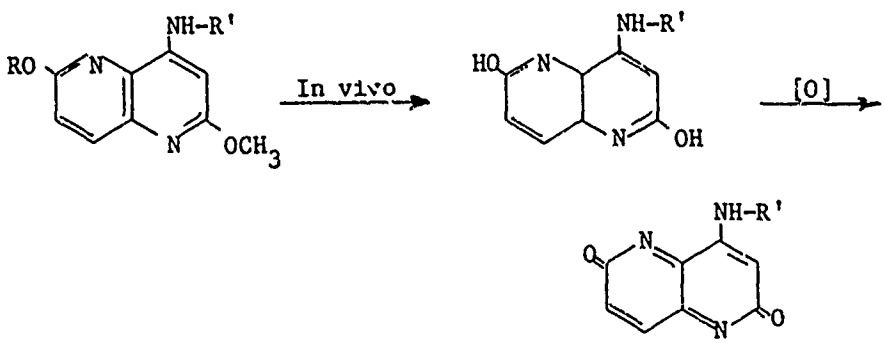
The title compounds which have been proposed for synthesis this year exhibit the following generalized structure:



As outlined in our original proposal (22), our primary reason for attempting their synthesis rests upon the reasoning that these 2,6-dialkoxy-4-amino-1,5-naphthyridines are the naphthyridine isosteres ("5-aza-8-amino-quinolines) of the highly active 2,6-dialkoxy-8-aminoquinolines,



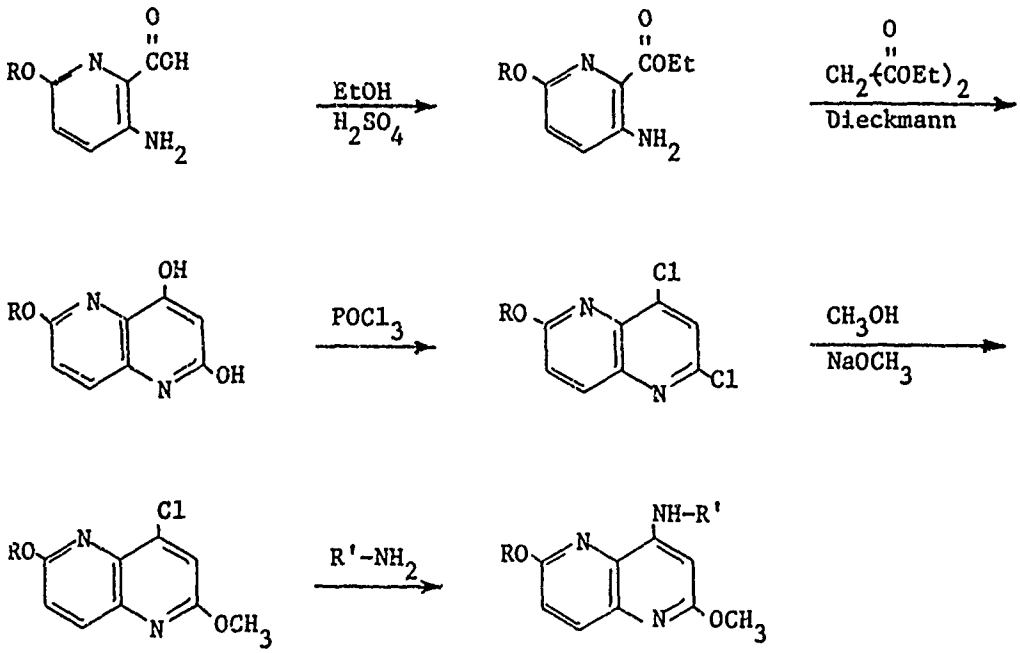
reported by Blanton (17c). As Blanton pointed out, Holmes speculated that the oxidative detoxification of quinine by rabbit liver, far from indicating as usually assumed, the advantage of blocking the 2-position of quinoline antimalarials, might equally well be construed as an argument in favor of deliberately introducing an oxygen at this position (42). Specifically, it appears that substances which are structurally related to the 8-amino-quinoline drugs, and which are both quinoline quinones and carbostyrils, might exhibit a desirable combination of low toxicity and high antimalarial activity. The title naphthyridines may, therefore, also lead to active quinoid structures in vivo as depicted below:



The primary synthetic route we have explored this year for the synthesis of the target 2,6-dialkoxy-4-amino-1,5-naphthyridines is outlined in Scheme 6 immediately below.

Scheme 6

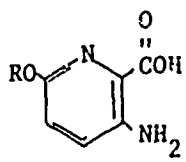
Synthetic Route to
2,6-Dialkoxy-4-Amino-1,5-Naphthyridines



Requisite in the procedure as outlined in Scheme 6 is the efficient preparation of the 6-alkoxy-3-aminopicolinic acid starting materials. Accordingly, a major effort for this year was focused upon the development of a useful synthetic route to these precursors. The results of these investigations, as well as the additional intermediates secured in accord with Scheme 6 are discussed in the subsections immediately below.

3.3.1 Preparation of 6-Methoxy-3-Aminopicolinic Acid

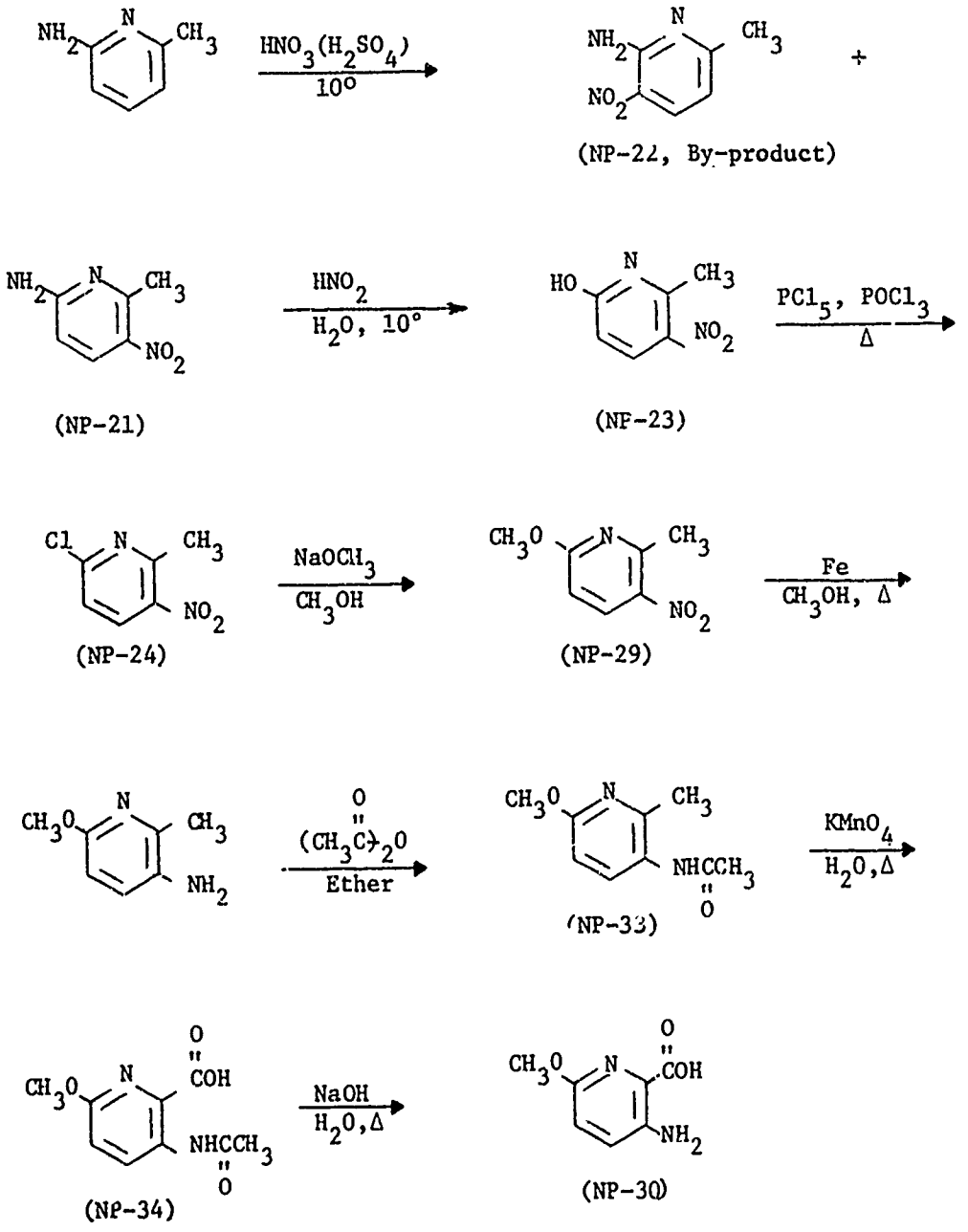
As stated in the introduction to this section, the overall synthetic scheme which we are employing to prepare the target 2,6-dialkoxy-4-amino-1,5-naphthyridines was outlined in Scheme 6. To our knowledge, however, the requisite 6-alkoxy-3-aminopicolinic acids,



have not been reported in the literature. This year we have successfully applied the procedure as outlined in Scheme 7 below as our first route to the formation of 6-methoxy-3-aminopicolinic acid (R = methoxy, above).

Scheme 7

Preparation of 6-Methoxy-3-Aminopicolinic Acid



The precursors shown in Scheme 7 which have been fully characterized this year, are included in Table 16 at the end of this section. The initial conversions shown in Scheme 7, through the formation of 6-chloro-3-nitro-2-picoline (NP-24), were performed essentially as described in the literature (36,37). It should be noted that the nitrogen analysis for 6-amino-3-nitro-2-picoline (NP-21) was consistently low. We have no rationalization for this result. Indeed, the complete analysis for this derivative was not reported in the original literature (36,37). Nevertheless, the spectra, analyses and physical constants of the ensuing derivatives were completely in agreement with the formulated structures.

In the next step, preformed 6-chloro-3-nitro-2-picoline (NP-24) was reacted with sodium methoxide in accord with Besley and Goldberg's procedure (38) to afford 6-methoxy-3-nitro-2-picoline (NP-29). This precursor was obtained analytically pure (Table 16) as yellow needles after recrystallization from pentane. Reduction of the nitro group was then conducted by the addition of NP-29 to a refluxing mixture of water, methanol, acetic acid, and iron powder. The amine was not purified at this stage, but was directly converted into the acetamido derivative in nearly quantitative yield by reaction with acetic anhydride in ether at room temperature. The resultant 6-methoxy-3-acetamido-2-picoline was converted into the corresponding picolinic acid with potassium permanganate in hot aqueous solution. Both the 6-methoxy-3-acetamido-2-picoline and 6-methoxy-3-acetamidopicolinic acid exhibited the reported melting points (39). The infrared spectra for both of these derivatives are included in Figures 56 and 57, respectively.

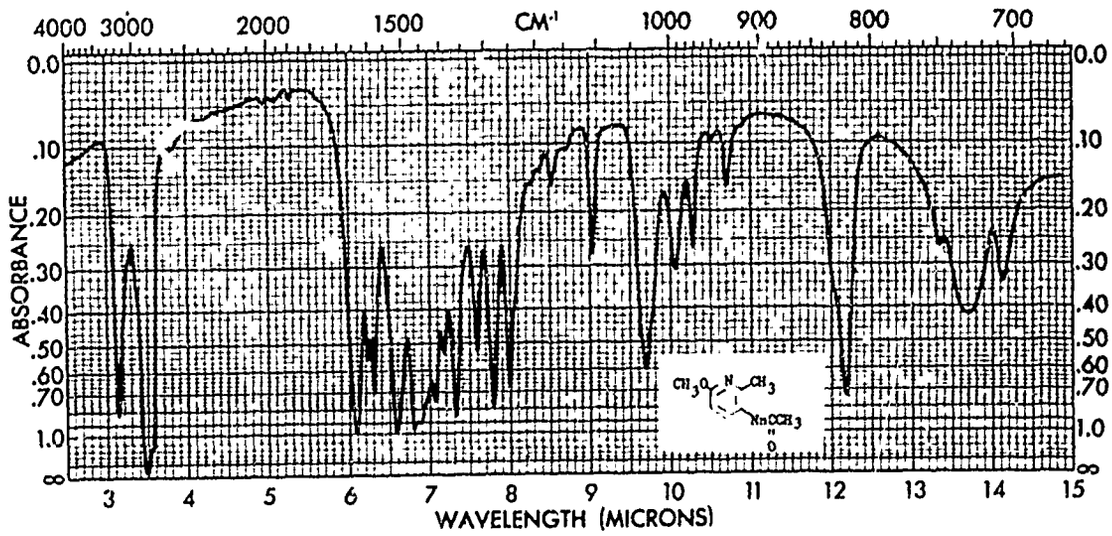


Figure 56. Infrared spectrum of 6-methoxy-3-acetamido-2-picoline (nujol mull)

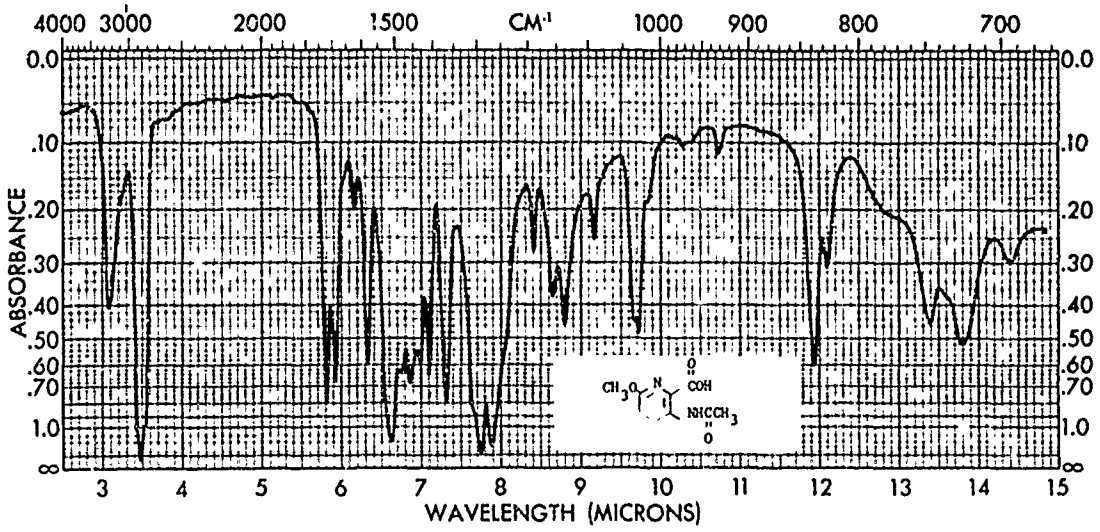


Figure 57. Infrared spectrum of 6-methoxy-3-acetamidopicolinic acid (nujol mull)

The final step in Scheme 7, hydrolysis of the acetamido linkage present in 6-methoxy-3-acetamidopicolinic acid was conducted by heating for a short period in refluxing 2.5 normal sodium hydroxide. After cooling to room temperature, neutralization of the reaction mixture afforded crude 6-methoxy-3-aminopicolinic acid (NP-30) as a tan powder in moderate yield. Somewhat surprisingly, the analytically pure acid (Table 16) could be obtained by high vacuum sublimation at 100-110°. The infrared spectrum of this acid is reproduced in Figure 58, and is clearly in accord with the formulated structure.

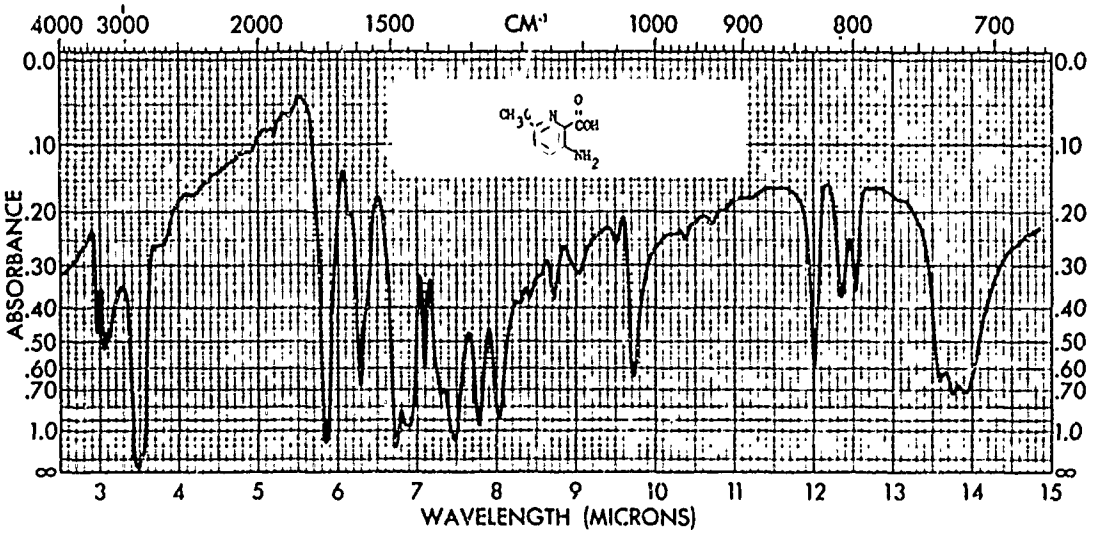


Figure 58. Infrared spectrum of 6-methoxy-3-aminopicolinic acid (nujol mull)

While the synthesis as described above affords a viable route to 6-methoxy-3-aminopicolinic acid, a somewhat more convenient procedure is described in the next section of this report.

Table 16

6-Methoxy-3-Aminopicolinic Acid Precursors

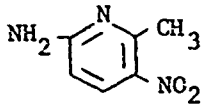
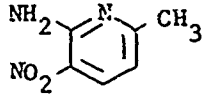
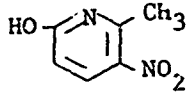
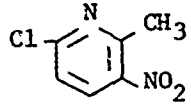
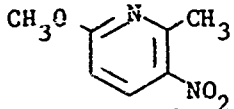
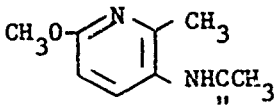
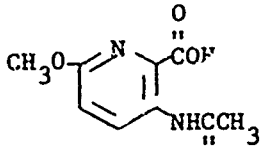
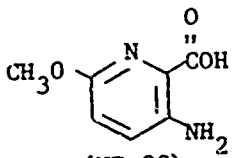
Structure	M.P., °C	Elemental Analysis C	H	N	
 (NP-21)	173-175	47.05 47.15	4.61 4.57	27.44 26.55	Theory Found
 (NP-22)	155-156	47.05 47.46	4.61 4.62	27.44 27.20	
 (NP-23)	241-242	46.75 47.22	3.93 3.91	18.18 18.00	
 (NP-24)	52-53	41.75 41.71	2.92 3.03	16.24[a] 15.95	

Table 16 (Cont'd.)

Structure	M.P., °C	Elemental Analysis C	H	N
 (NP-29)	67-68	50.00 50.27	4.79 4.93	16.66 17.08
 (NP-33)	132-133	59.98 60.44	6.71 6.69	15.55 15.40
 (NP-34)	193-194	51.41 51.53	4.80 4.62	13.33 13.40
 (NP-30)	135-136	50.00 50.26	4.79 4.76	16.66 16.61

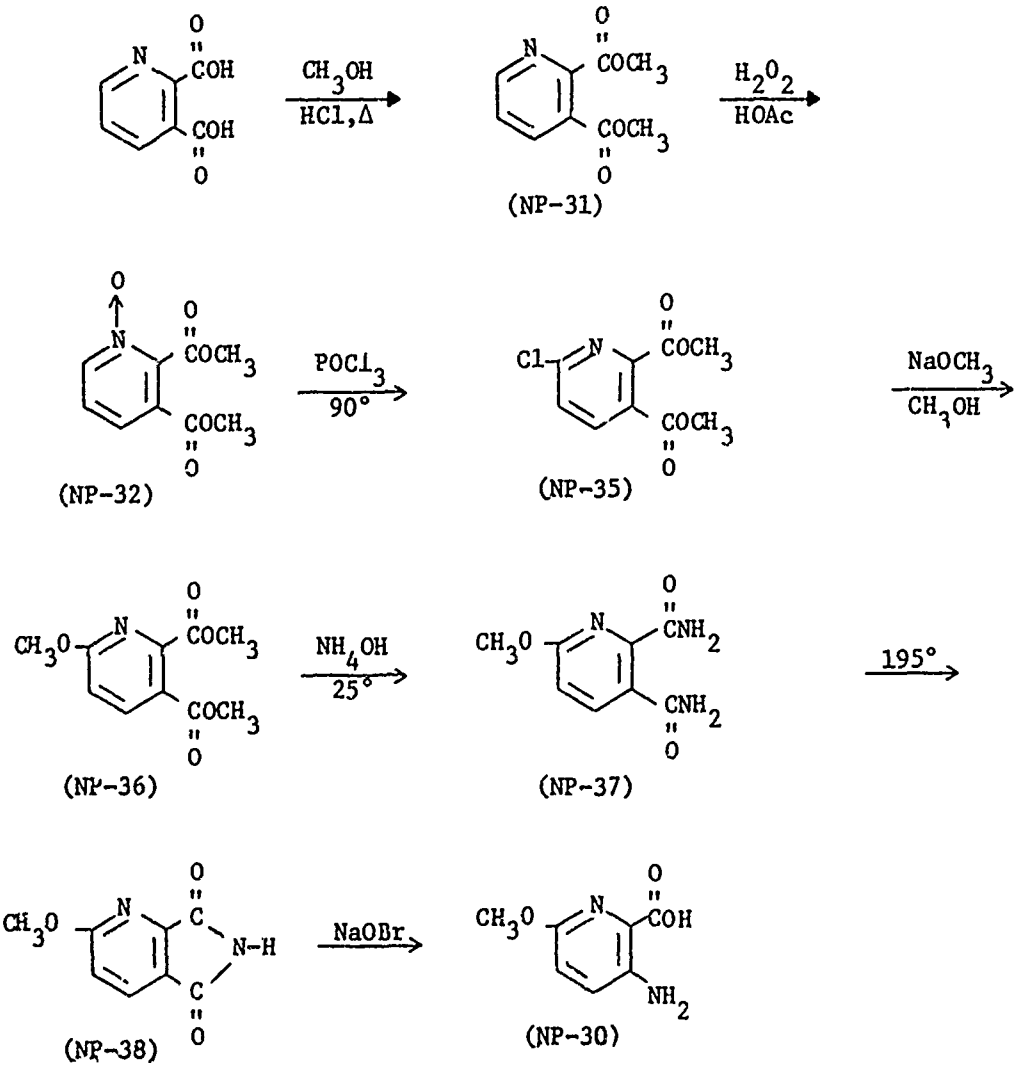
(a) Theory for Cl = 20.55, Found = 20.15.

3.3.2 Alternative Preparation of 6-Methoxy-3-Aminopicolinic Acid

Our first synthetic approach to the preparation of 6-methoxy-3-aminopicolinic acid was described in full detail in the preceding section. However, many of the steps involved in this synthetic route were either non-scalable or involved the tedious separation of isomers. Accordingly, this year we have developed an alternative synthetic route to this requisite precursor as outlined in Scheme 8. While the use of this procedure has already afforded 6-methoxy-3-aminopicolinic acid, a variety of 6-alkoxy substituents may also be introduced into the pyridine ring with the use of different alkoxides in the fourth step of Scheme 8.

Scheme 8

Alternative Synthesis of 6-Methoxy-3-Aminopicolinic Acid



Each of the precrusors listed in Scheme 8 which were characterized this year are included in Table 17 at the end of this section along with their physical constants and full analytical data.

In the first step of Scheme 8, quinoline acid was converted to its dimethyl ester (NP-31) employing an acidic methanol reaction medium (39). The next three precursors, dimethyl quinolinate N-oxide (NP-32), dimethyl 6-chloroquinolinate (NP-35), and dimethyl 6-methoxyquinolinate (NP-36), were also prepared essentially as described in the literature (40). The proton spectra for NP-35 and NP-36 are reproduced in Figures 59 and 60, respectively. While it is possible that the initial Meisenheimer reaction could lead to a mixture of isomers (41), inspection of Figures 59 and 60 reveals that the chloro and methoxy functionality were cleanly introduced into the ring-6 position.

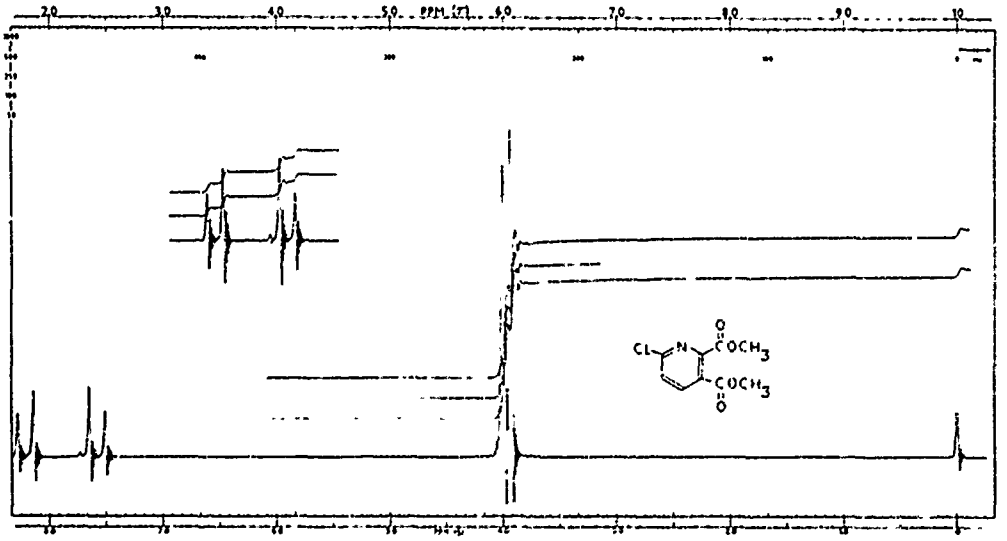


Figure 59. Proton spectrum of dimethyl 6-chloroquinolinate ($CDCl_3$)

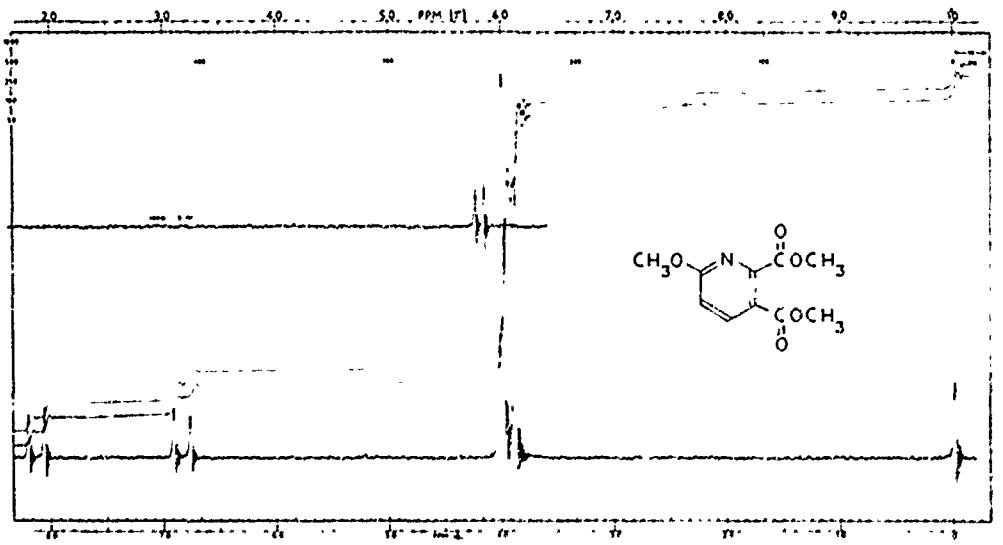
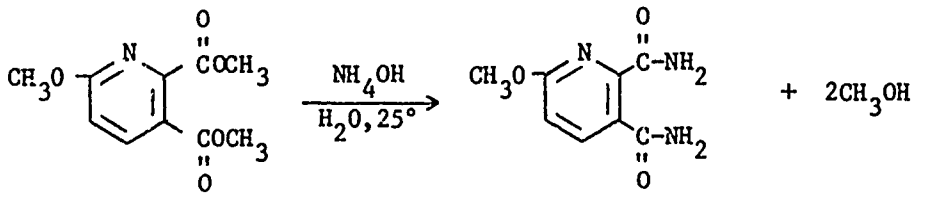


Figure 60. Proton spectrum of dimethyl 6-methoxyquinolinate ($CDCl_3$)

Conversion of dimethyl 6-methoxyquinolinate (NP-36) to its corresponding bis-amide (NP-37) was effected in concentrated ammonium hydroxide at room temperature.



The initial thin suspension of the diester gradually thickened over a period of several hours as the bis-amide separated from solution. The crude bis-amide could then be isolated in nearly quantitative yield by removal of the solvent under a strong nitrogen stream. The crude 6-methoxyquinolindiamide thus obtained exhibited an infrared spectrum virtually identical to the analytically pure product (Figure 61).

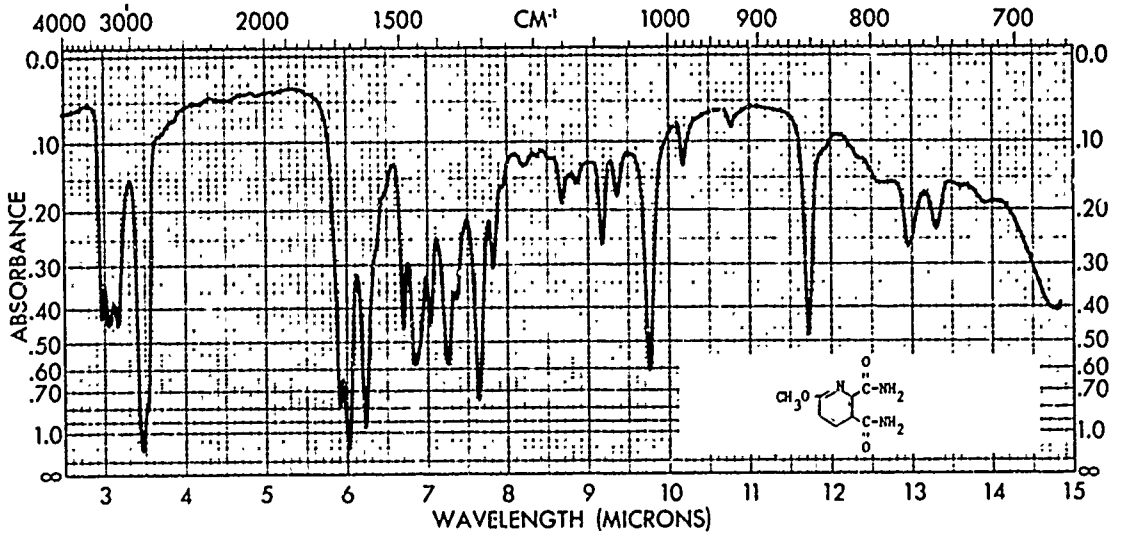
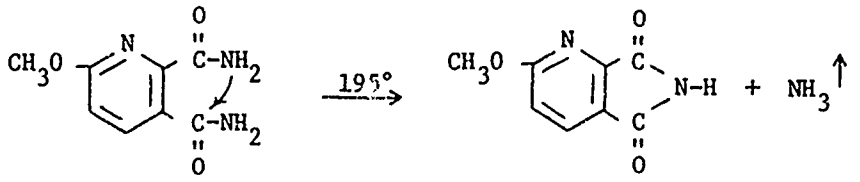


Figure 61. Infrared spectrum of 6-methoxyquinolindiamide (nujol mull)

The next step, conversion of the bis-amide (NP-37) into the imide (NP-38), was conducted thermally by slowly heating the bis-amide to a temperature 25° below its melting point. The evolution of ammonia was fairly fast at 195° (pH paper), and heating was continued until no further ammonia was given off.



The crude imide was thereby obtained in nearly quantitative yield. The infrared spectrum for the pure 6-methoxyquinolinimide (glacial acetic acid) is reproduced in Figure 62.

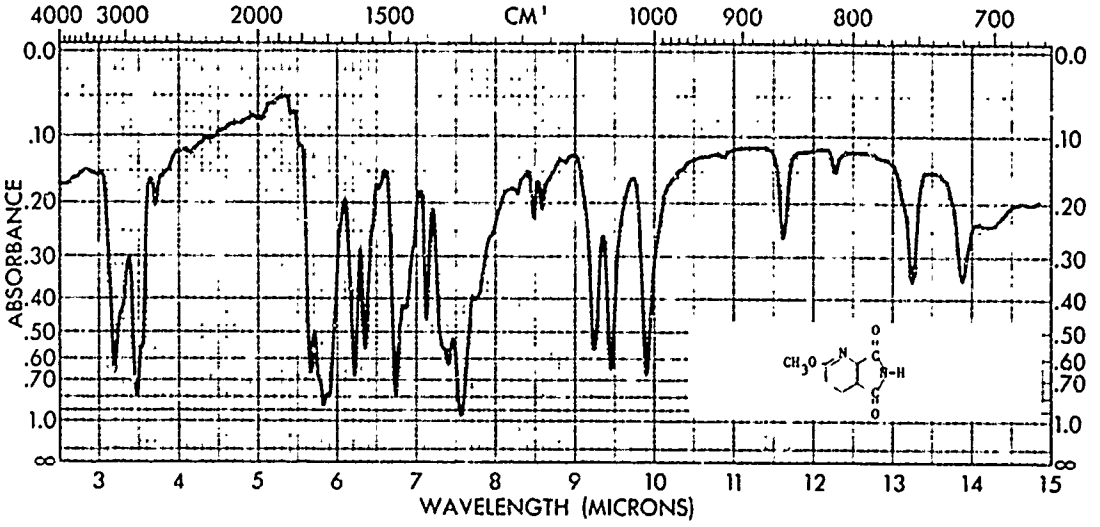
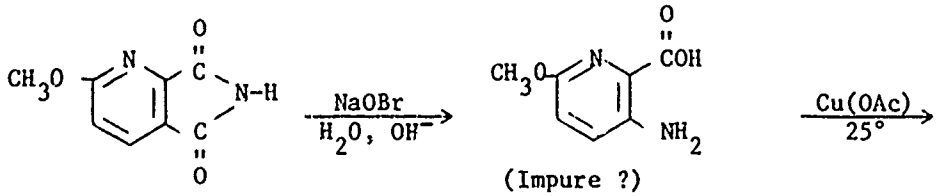
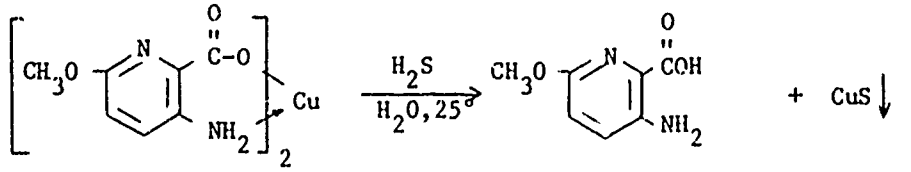


Figure 62. Infrared spectrum of 6-methoxyquinolinimide (nujol mull)

The Hoffmann degradation of 6-methoxyquinolinimide proceeded smoothly. While none of the isomeric 2-amino-6-methoxynicotinic acid was observed in this reaction, nevertheless, the crude acid was purified through the intermediacy of its copper salt (NP-39).



(Impure ?)



(Pure)

An analytical sample of the copper salt was prepared by trituration with hot water and drying at 110°. The infrared spectrum for this salt is reproduced in Figure 63. The pure 3-amino-6-methoxy-picolinic acid was then isolated by suspending the copper salt in water and bubbling hydrogen sulfide through the suspension for several hours. After filtration of the copper sulfide, removal of solvent afforded the acid in a high state of purity. The configuration of this acid was confirmed by elemental analysis (see Experimental) as well as by direct comparison of its physical and spectral properties with the acid produced by an unambiguous route as described in the preceding section (NP-30).

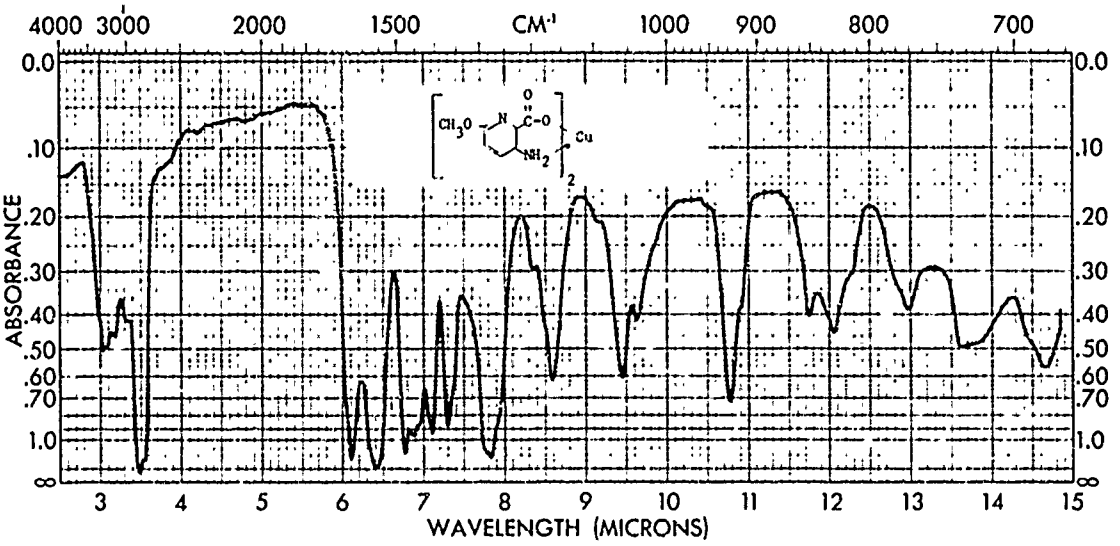


Figure 63. Infrared spectrum of cupric 3-amino-6-methoxypicolinate (nujol mull)

Table 17

2,6-Dialkoxy-4-Amino-1,5-Naphthyridine Precursors

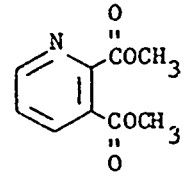
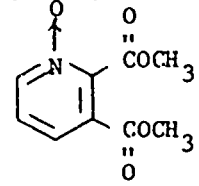
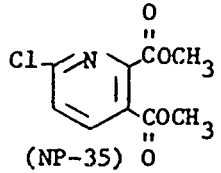
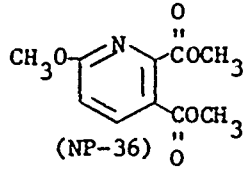
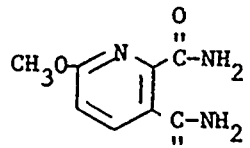
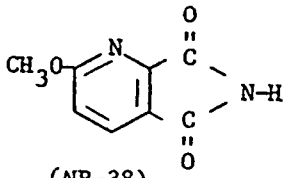
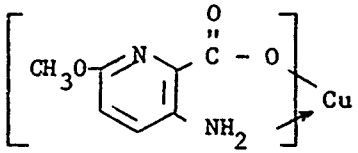
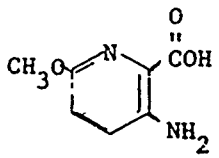
Structure	M.P., °C B.P., °C(mm)	Elemental Analysis C	 H	 N	
 (NP-31)	50-52	55.38 55.11	4.65 4.67	7.18 7.01	Theory Found
 (NP-32)	142-144	51.19 51.42	4.30 4.20	6.63 6.52	
 (NP-35)	111-115(0.2)	47.07 46.92	3.51 3.55	6.10 6.19	
 (NP-36)	62-63	53.33 53.41	4.92 4.80	6.22 6.22	

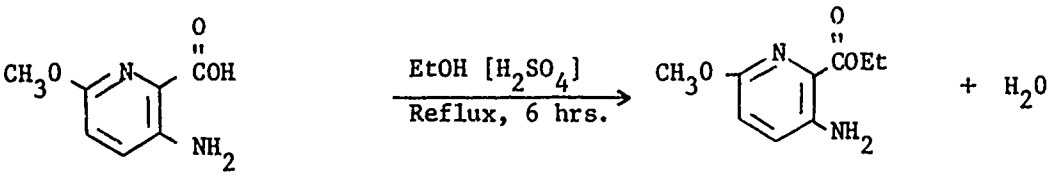
Table 17 (Cont'd.)

Structure	M.P., °C B.P., °C(mm)	Elemental Analysis C	 H	 N
 (NP-37)	220-220.5	49.23 49.32	4.65 4.75	21.53 21.55
 (NP-38)	272-273	53.93 53.99	3.40 3.37	15.73 15.64
 (NP-39)	>300	42.26 42.07	3.55 3.62	14.08 13.81
 (NP-30, via Hoffmann Deg.)	137.5- 139	50.00 49.84	4.79 4.89	16.66 16.63

3.3.3 Naphthyridine Intermediates

At the time this report was written, we are currently involved in the final steps of the synthetic procedure as outlined in Scheme 6. The intermediates which have been characterized to date in conjunction with our synthetic studies directed at the formation of the target 2,6-dialkoxy-4-amino-1,5-naphthyridines are included in Table 18 at the end of this section.

In the first step of Scheme 6, the conversion of 3-amino-6-methoxypicolinic acid to its corresponding ethyl ester was conducted employing ethanol and concentrated sulfuric acid at reflux.



The crude ester was isolated in 60% yield and its spectral properties were identical to the analytical sample obtained by recrystallization from heptane (NP-40, Table 18). The appearance of a carbonyl absorption near 6.0μ in the infrared spectrum of this ester is noteworthy (Figure 64). However, the proton spectrum (Figure 65) is completely in accord with the formulated structure. The appearance of a sharp methoxy singlet at 6.09τ reveals that no methyl group migration from the ring-6 ether linkage to the ring nitrogen has occurred in this step.

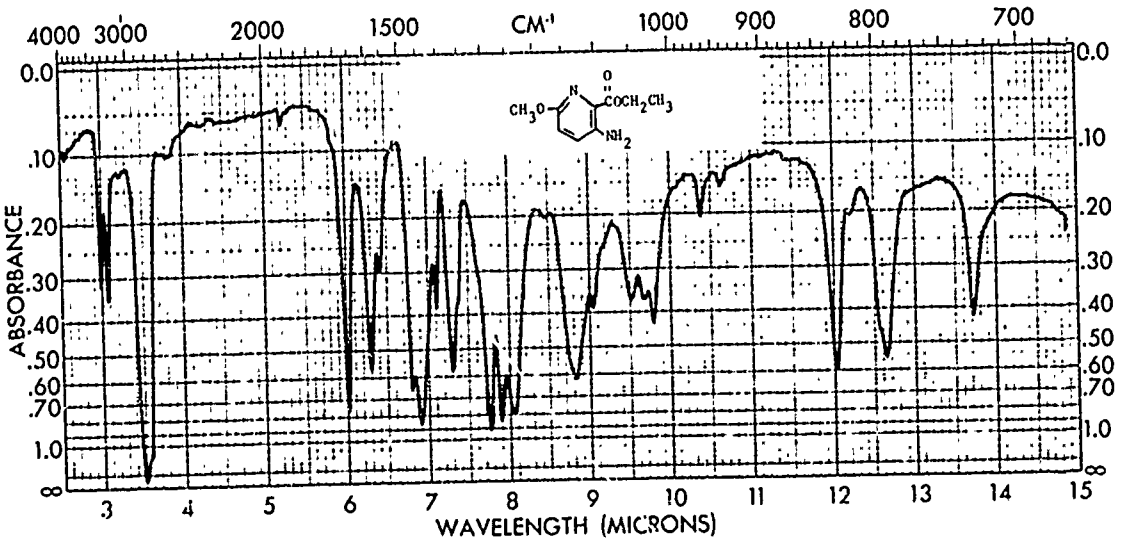


Figure 64. Infrared spectrum of ethyl 6-methoxy-3-aminopicolinate (nujol mull)

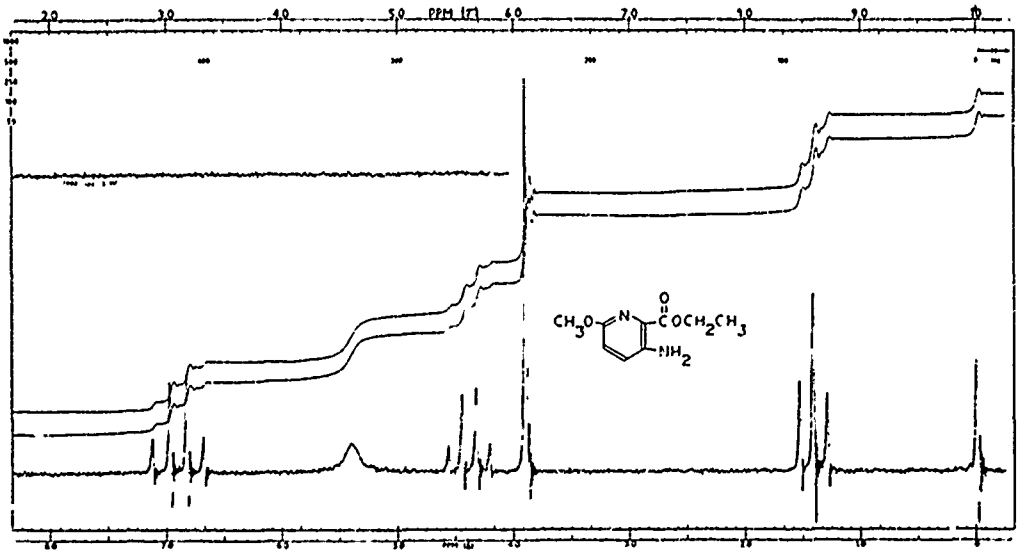
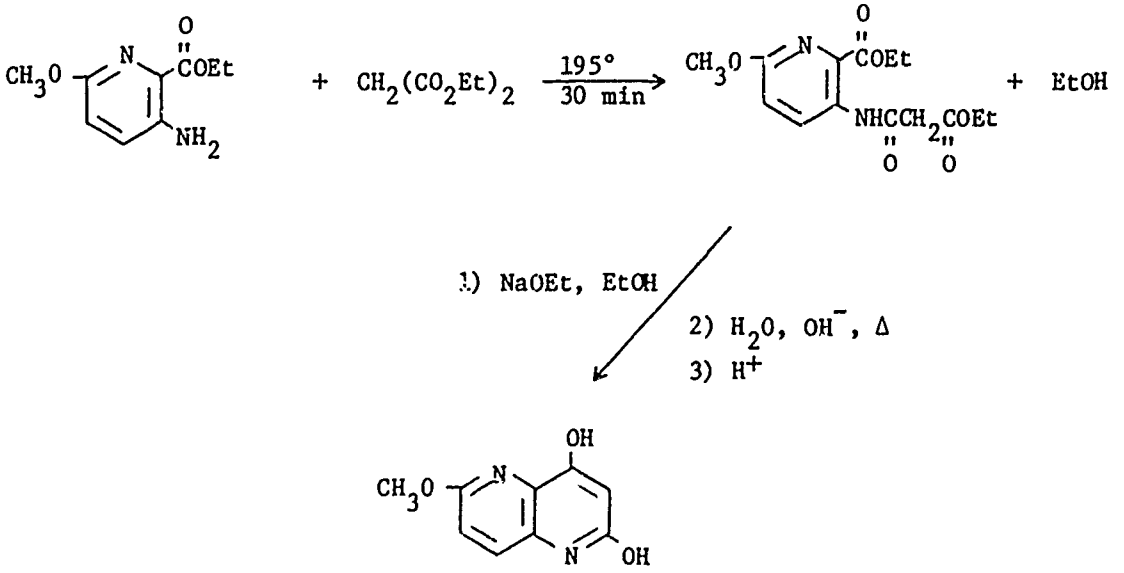


Figure 65. Proton spectrum of ethyl 6-methoxy-3-aminopicolinate ($CDCl_3$)

The Dieckmann cyclization of ethyl 3-amino-6-methoxy-picolinate (NP-40) was conducted by first condensing this ester with diethyl malonate at 195°. The intermediary malonamic ester was not isolated but was directly cyclized to the 2,4-dihydroxy-6-methoxy-1,5-naphthyridine.



The overall yield of the crude dihydroxy compound was 51%. Its infrared spectrum is reproduced in Figure 66, and the conspicuous presence of a strong carbonyl band near 6.0μ reveals that the tautomeric naphthyridone structure is preferred in the solid state (19). An analytical sample (NI-36, Table 18) was prepared by trituration with hot water; however, the crude product was sufficiently pure for the next step of this synthesis.

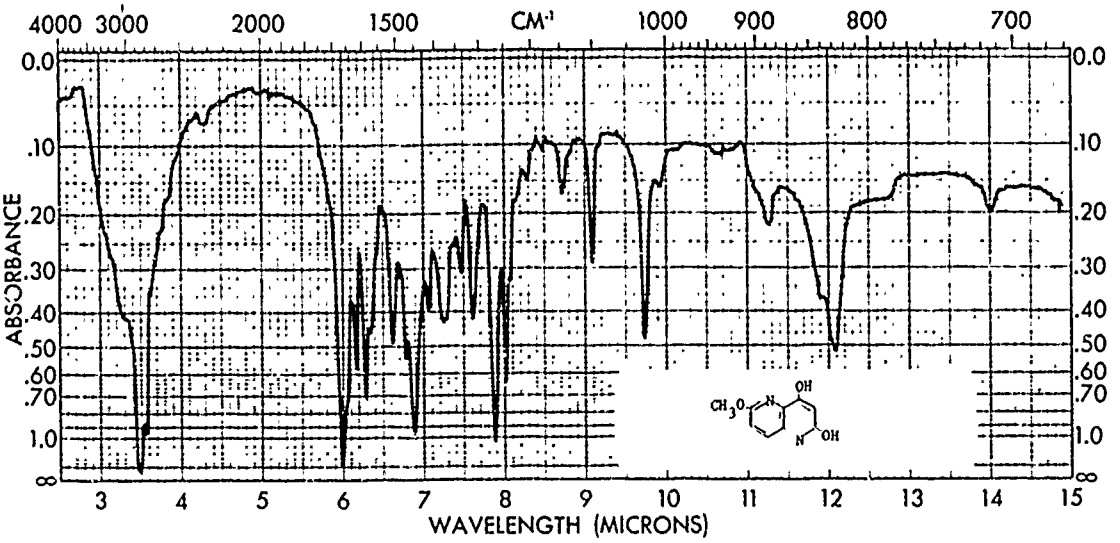
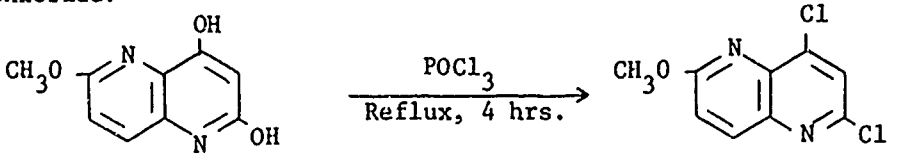


Figure 66. Infrared spectrum of 6-methoxy-2,4-dihydroxy-1,5-naphthyridine (nujol mull).

Conversion of the dihydroxy compound to the corresponding dichloro derivative was conveniently effected with the use of phosphorus oxychloride.



After workup, the analytically pure 2,4-dichloro-6-methoxy-1,5-naphthyridine (NI-37) was isolated as a white solid in 80% yield. Its proton spectrum is reproduced in Figure 67 and is clearly in accord with the formulated structure.

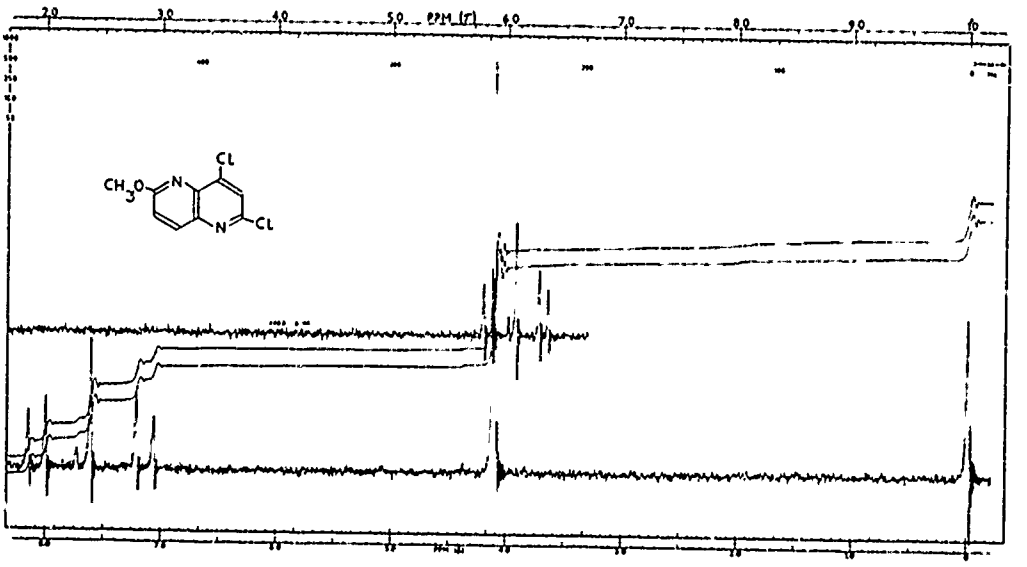
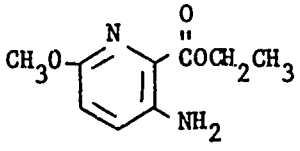
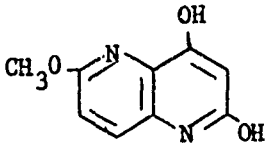
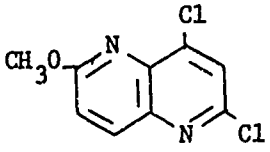


Figure 67. Proton spectrum of 2,4-dichloro-6-methoxy-1,5-naphthyridine ($CDCl_3$)

At present, we are currently involved with the succeeeding steps as outlined in Scheme 6. The results of these investigations will be fully discussed in our next annual report.

Table 18

2,6-Dialkoxy-1,5-Naphthyridine Intermediates

Structure	M.P., °C	Elemental Analysis C	H	N	
 (NP-40)	79-81	55.09 55.25	6.17 6.21	14.28 14.12	Theory Found
 (NI-36)	288-290	56.25 56.06	4.19 4.18	14.58 14.27	
 (NI-37)	143-143.5	47.19 46.75	2.64 2.63	12.23[a] 12.61	

(a) Theory for Cl = 30.96; Found = 30.65

4. EXPERIMENTAL

The experimental procedures used to prepare each of the precursors, intermediates and target 4-amino-1,5-naphthyridines which were submitted to WRAIR this year are explained in detail below. The synthetic procedures are listed numerically according to the code designation assigned to each compound. The Naphthyridine Precursors (NP-1 through NP-43), Naphthyridine Intermediates (NI-1 through NI-41), and Naphthyridine Targets (NT-1 through NT-19) are included in Sections 4.3, 4.4 and 4.5, respectively.

4.1 Commercial Chemicals

All chemicals were of reagent grade and were purchased from a variety of commercial sources including Aldrich Chemical Company, Cedar Knolls, New Jersey; Eastman Kodak Company, Rochester, New York; Ace Scientific Supply Co., Inc., Linden, New Jersey; Matheson, Coleman and Bell East Rutherford, New Jersey; ICN-K&K Laboratories, Inc., Plainview, New York; PCR, Inc., Gainesville, Florida; Chemicals Procurement Laboratories, Inc., College Point, New York; Pfaltz and Bauer, Inc., Flushing, New York; Columbia Organic Chemicals Company, Inc., Columbia, South Carolina; Alfa-Ventron, Inc., Beverly, Massachusetts; J. T. Baker Chemical Company, Phillipsburg, New Jersey; and Matheson Gas Products, East Rutherford, New Jersey. All of the starting materials were used as received unless otherwise noted.

4.2 Physical, Spectral and Analytical Methods

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Infracord Spectrophotometer (Model 137) using sodium chloride optics. Liquid samples were run as thin films and solid derivatives were run as nujol mulls versus air. Proton NMR spectra were determined with a Varian Associates A-60 spectrometer; samples were either run neat or in deuterochloroform solutions at room temperature. Chemical shift values are expressed in tau (τ) units versus internal tetramethyl silane as standard (10.0 τ). Refractive indices were carried out at 20-25° employing a thermostated Zeiss refractometer. Elemental analysis for carbon, hydrogen, nitrogen, chlorine and fluorine were performed by the Analytical and Information Division, Esso Research and Engineering Company, Linden, New Jersey.

4.3 Naphthyridine Precursors (NP-1 through NP-43)

2-Alkoxy-5-nitropyridines (NP-1 thru NP-5)

The title precursors (2-alkoxy substituent = methyl, n-butyl, n-decyl and 2,2,2-trifluoroethyl) were prepared as Friedman has described in detail for the n-butoxy analog (7). After work-up, the n-butyl derivative was obtained as a distillable liquid. The remaining three precursors were obtained as solids after removal of the solvent and recrystallization

of the residues from methanol (charcoal). The yields of the methyl, n-butyl and 2,2,2-trifluoroethyl derivatives were ca., 80%; the n-decyl compound was obtained in a slightly lower yield of 50%. The appropriate analytical data are included in Table 1. The 2-(p-chlorobenzyoxy) analog was prepared via a modified procedure and is explained in detail below.

Solid p-chlorobenzyl alcohol (93.0g, 0.651 mole) was added portionwise to the suspension of sodium ethoxide (44.0g, 0.648 mole) in 1ℓ of tetrahydrofuran at room temperature. The mixture was then slowly heated to 50° and maintained at this temperature for about three hours. The orange suspension was then cooled to room temperature, and 2-chloro-5-nitropyridine (103.0g, 0.650 mole) was slowly added as a solid. The moderate exotherm was controlled with the aid of an external water bath. The mixture was heated to reflux for three hours and cooled. The brown-orange reaction mixture was filtered and solvent removed from the filtrate to afford crude product as a brownish solid. Pure 2-(p-chlorobenzyloxy)-5-nitropyridine was obtained in 35% yield (60.0g) by recrystallization from methanol. Alternatively, the crude product could be obtained more easily (ca., 25% yield) by adding an excess of methanol to the clear THF filtrate. The analytical sample (Table 1) was recrystallized from methanol (charcoal) and was obtained as small, colorless needles. The proton spectrum is reproduced in Figure 2.

5-Amino-2-Alkoxypyridines (NP-6 thru NP-9)

Friedman's general procedure was applied to the preparation of these precursors (7). The overall yields of the free amines ranged from 50 to 90% and were not optimized. Two of these derivatives (the n-butoxy and n-decyloxy) eluded analytical characterization of the free bases. These two derivatives were, therefore, converted in nearly quantitative yields to their dihydrochlorides in ether and were characterized as such. The specific preparation of 5-amino-2-(p-chlorobenzyloxy) pyridine is described below.

A mixture of methanol (125g), water (125g), glacial acetic acid (5 ml) and iron powder (100g) was heated to reflux. Solid 2-(p-chlorobenzyloxy)-5-nitropyridine (50g) was added slowly such that the reflux returned to the reaction flask. The total addition time was about 1.5 hours. After refluxing overnight, the mixture was present as a deep black suspension. The mixture was cooled, and 10 ml. of 20% aqueous sodium hydroxide added with stirring. This mixture was then filtered, and the filter cake washed well with methanol. The combined filtrates were stripped on a rotary evaporator until all of the methanol was removed. The resultant suspension was extracted with ether, and the combined ether layers dried with magnesium sulfate. After removal of solvent, the crude amine was obtained as a pale brown, crystalline solid in 65% yield (28.9g). The analytical sample (Table 2) was obtained as colorless plates from ether (charcoal)-pentane and exhibited a sharp melting point of 89-90°. The proton spectrum is reproduced in Figure 4, and the following assignments have been made. NMR ($CDCl_3$): 2.40 τ (1 H, d, ring h-6); 2.71 τ (4H, s, p-Cl ring); 3.04 τ (1H, q, ring h-4); 3.40 τ (1H, d, ring H-3); 4.76 τ (2Hm sm O CH_2); 6.62 τ (2H, s, NH_2); $J_{3,4}$=8.7 Hz, and $J_{4,6}$= 3.0 Hz.

Diethyl 6-Alkoxy-3-Pyridylaminomethylenemalonates (NP-10 thru NP-13)

The title precursors were obtained in quantitative yields by the following general procedure. The appropriate amine (NP-6 thru NP-9) was slowly added neat into one mole-equivalent of diethyl ethoxymethylenemalonate with efficient stirring at room temperature. The slight exotherm was controlled with the aid of an external water bath. The mixture was then heated to 100° for one hour, and the ethanol produced in the reaction was allowed to escape through a short air condenser. After cooling to room temperature, the crude products solidified upon standing for several hours. In most instances, the crude materials were sufficiently pure for the next step. The analytical samples (Table 3) were obtained by recrystallization from methanol (charcoal), ethanol, or isopropanol-pentane.

Quinolinimide (NP-14)

Sucharda's procedure was utilized for the preparation of quinolinimide (25). Quinolinic acid (450g, 2.69 mole) was added all at once to 500g of acetic anhydride. The suspension was slowly heated with stirring, and acetic acid was distilled over a period of about three hours. When the internal temperature rose to 160°, the distillation was stopped and the mixture cooled to 100°. Additional acetic anhydride was then added (240g), and the mixture cooled to 100°. Additional acetic anhydride was then added (240g), and the mixture cooled to room temperature with stirring. Acetamide (280g, 4.75 mole) was quickly added, and the mixture maintained at 120-125° overnight. After cooling to room temperature, the suspension was filtered to afford crude quinolinimide as a gray-brown solid. Purification was then effected according to the improved procedure (26). The crude product was triturated with 1ℓ of acetic acid at 60°, and the filtered solid was suspended in about 2ℓ of hot water. After filtration and air-drying, the quinolinimide was obtained as a light gray-brown solid in 44% yield (176g). The analytical sample (Table 11) was obtained from acetic acid (charcoal) and melted 11-12° higher than reported by Sucharda (25).

Cupric 3-Aminopicolinate and 3-Aminopicolinic Acid (NP-15 and NP-16)

The title derivatives were prepared essentially as described in the literature (27). Sodium hypobromite was preformed by the dropwise addition of bromine (112g) into an ice-cold solution of sodium hydroxide (230g of 50% soln.) in 600 ml. of water. The cold hypobromite solution was then added dropwise into an ice-cold solution of quinolinimide (100g) in 1,800 ml. of water containing sodium hydroxide (400g of 50% solution). The total time for the addition was about three hours. The mixture was then warmed to room temperature for one hour, and then heated to 85° for an additional hour. After cooling to room temperature, the pH was adjusted to 5 with 50% sulfuric acid (ca., 300 ml). The mixture was then cooled in an ice-bath for several hours: a suspension formed (mostly sodium sulfate) which was filtered cold. The clear, light-amber filtrate was warmed to room temperature and vigorously stirred while a solution of cupric acetate (40g),

glacial acetic acid (20 ml.) and water (800 ml) was added dropwise. The copper salt immediately separated from solution as a blue-gray suspension. This suspension was filtered, the salt washed well with water and finally vacuum dried overnight. The crude yield of the moist copper salt was about 130g. The analytical sample (Table 11) was obtained by repeatedly triturating with hot water and drying at 110° (0.10 mm) for three hours.

For the preparation of 3-aminopicolinic acid, the combined cupric 3-aminopicolinates produced from 275g of quinolinimide (1.86 mole) were suspended in about 3ℓ of water at room temperature. Gaseous hydrogen sulfide was then slowly bubbled through over a period of 1.5 hours. The resultant black suspension was filtered to remove the cupric sulfide. Crude 3-aminopicolinic acid was isolated in several crops by removing most of the water and cooling. The yield of the crude acid was 143g (56%) after drying at 110° (0.10 mm) for fifteen hours. The analytical sample (Table 11) was obtained as a pale beige, crystalline solid by recrystallization from water and drying at 110°. The melting point for this material was was ca., 10-15° higher than that reported in the literature (28).

Ethyl 3-Aminopicolinate (NP-17)

The procedure of Oakes was employed to prepare the title precursor (27). A suspension of 3-aminopicolinic acid (23.0g, 0.167 mole) in sulfuric acid (46g) and ethanol (46g) was refluxed for a period of about ten hours. The resultant clear, yellow solution was cooled to room temperature and slowly poured onto 200g of ice with vigorous stirring. After warming to room temperature, the solution was brought to pH 9 by the addition of con. ammonium hydroxide (ca., 50g). At this point, a white suspension formed. The suspension was repeatedly extracted with ether (1.5ℓ) until only a clear aqueous phase was present. The ether layers were dryed over magnesium sulfate, concentrated, and cooled to afford analytically pure ethyl 3-aminopicolinate (Table 11) as colorless needles (11.9g, m. pt., 131-132°). A second crop was obtained to afford a combined yield of 61% (16.8g).

2-Ethoxy-5-nitropyridine (NP-18)

Solid sodium ethoxide (93.0g, 1.37 mole) was dissolved in 1.7ℓ of absolute ethanol at room temperature, and 2-chloro-5-nitropyridine (214.0g, 1.35 mole) was added portionwise with cooling. The resulting mixture was stirred overnight at room temperature before heating to reflux for three hours. After cooling to room temperature, the suspension was filtered hot. The title product quickly separated from the ethanol during the filtration. Consequently, the filter cake was repeatedly extracted with hot methanol and filtered as quickly as possible while still hot. The combined filtrates were evaporated to about one-half of their original volume and then cooled. The title product was then isolated in several crops as a light tan, crystalline solid in 65% yield (148g). The analytical sample (Table 1) was recrystallized from ethanol-charcoal and was obtained as colorless crystals.

3-Amino-6-ethoxypyridine

A mixture of methanol (400 ml.), water (400 ml.), glacial acetic acid (16 ml.) and iron powder (320g) was heated to a gentle reflux. Solid 2-ethoxy-5-nitropyridine (147.5g, 0.876 mole. NP-18) was then slowly added over a period of two hours. The rate of addition was limited by the fairly rapid increase in the reflux ratio as each portion of the nitro compound was added. The mixture was then maintained at reflux overnight before cooling to room temperature. A 20% solution of sodium hydroxide (33 ml.) followed by 167 ml. of water was then stirred in at room temperature. The black suspension was filtered, and the filter cake washed repeatedly with methanol. Methanol was stripped from the combined filtrates to afford a two-phase system. The organic layer was extracted with ether, dried over magnesium sulfate, and solvent removed under a nitrogen purge. The crude amine was obtained as a brown oil in 66% yield (80.0g), and was judged to be pure enough for the next step (vide infra).

Diethyl 6-ethoxy-3-pyridylaminomethylenemalonate (NP-19)

Crude 3-amino-6-ethoxypyridine (80.0g, 0.578 mole) was slowly added neat to one mole-equivalent of diethyl ethoxymethylenemalonate at room temperature. The resultant thick slurry was then heated to 100° and maintained at that temperature for one hour. After cooling to room temperature, the crude product solidified and was obtained as a tan solid in quantitative yield. The analytical sample (Table 3) was obtained as a white, amorphous solid after recrystallization from heptane-charcoal. The proton spectrum for this precursor is reproduced in Figure 5.

Diethyl 6-n-decyl-3-pyridylaminomethylenemalonate (NP-20)

Preformed 2-n-decyloxy-5-aminopyridine (4.80g, 19.2 mmole, 7) was slowly added as a solid into diethyl ethoxymethylenemalonate (4.15g, 19.2 mmole). A moderate exotherm was observed, and a brownish suspension formed. The mixture was then heated to 120° for one hour and the ethanol produced in the reaction was allowed to escape through a short air condenser. After cooling to room temperature, the crude product quickly solidified and was obtained in quantitative yield as a brownish solid. The analytical sample (Table 3) was obtained by recrystallization from pentane (charcoal) and proved to be a white, fluffy powder.

6-Amino-3-nitro-2-picoline (NP-21) and
6-Amino-5-nitro-2-picoline (NP-22)

The procedure as described in the literature was used to prepare the title precursors (36,37). Molten 6-amino-2-picoline (25.4g, 0.235 moles) was slowly added dropwise into 120 ml. of sulfuric acid surrounded by an ice-bath (temperature = 0-5°). When this very exothermic addition was completed, a cooled mixture of 17.5 ml. of sulfuric acid and 17.5 ml. of nitric acid were slowly added to the mixture maintained at 0-5°. Stirring was continued at 0-5° for an additional hour before warming to room temperature and stirring overnight. The mixture was then heated to 60° for one

hour and finally to 100° for another hour before cooling. The contents of the flask were then slowly poured onto 500g. of ice. After warming to room temperature, the acid mixture was neutralized to a pH of 5-6 by the slow addition of 50% sodium hydroxide (ca., 260 ml). The precipitated solids were then quickly filtered (before much sodium sulfate precipitated) and air dryed overnight. The crude brown powder was then slowly steam distilled until no yellow color was observed in the distillate. The steam volatile isomer quickly separated from the cooled distillates. This product was the 5-nitro isomer (NP-22) which was obtained in low yield as yellow needles after recrystallization from ethanol (charcoal) at -20°. The non-volatile isomer was obtained in a crude yield of 17g (47%) by filtration of the residual water. This isomer (6-amino-3-nitro-2-picoline, NP-21) was obtained in an overall yield of 14g as a light yellow powder after recrystallization from ethanol (charcoal) at -20°. The analytical data of this solid (Table 16) repeatedly exhibited a low value for the nitrogen analysis.

6-Hydroxy-3-nitro-2-picoline (NP-23)

As reported by Baumgarten and Su (37), 6-amino-3-nitro-2-picoline (29.9g, 0.195 mole, NP-21) was slowly added at room temperature to a mixture of concentrated sulfuric acid (35 ml) and 500 ml. of water. After stirring for one hour at 25°, 150g. of ice was added and the mixture cooled to 10°. A solution of sodium nitrite (20g, 0.29 moles) in 60 ml. of water was then added dropwise. Stirring was then maintained at 10° for one hour. The precipitated solid was then filtered, water washed and finally air-dryed to afford the title precursor in a crude yield of 23g. (77%). The analytical sample (Table 16) was recrystallized from methanol (charcoal) and was dried at 25° (0.10 mm).

6-Chloro-3-nitro-2-picoline (NP-24)

As reported by Baumgarten and Su (37), 6-hydroxy-3-nitro-2-picoline (20.0g, 0.130 mole, NP-23) was added as a solid into a stirred mixture of phosphorus pentachloride (8.0g.) and phosphoryl chloride (4cc) at 25°. The thick mixture was then heated to 110° for three hours and then cooled to 25°. Additional phosphorus pentachloride (5g) and phosphoryl chloride (5cc) were added and the fluid, brown mixture again heated to 110° for one hour before cooling. The contents of the flask were then slowly poured onto 500g. of ice and 1ℓ. of water. The suspension was filtered and the crude product air-dryed overnight. After recrystallization from ethanol (charcoal), the title precursor was obtained as light yellow needles in an overall yield of 49% (11.0g, m.pt., 52-53°). The analytical data for this sample are included in Table 16.

3-Amino-6-chloropyridine (NP-25)

In accord with the procedure as reported in the literature (18), a suspension of iron powder (400g) in 600 ml of water was heated to 90° with stirring. Note: Much higher yields of product can be achieved by running the reduction at 100°. Solid 2-chloro-5-nitropyridine was then added portionwise over a three hour period, and the mixture maintained at

this temperature for an additional two and one-half hours. The hot suspension was then filtered and the cake repeatedly washed with hot water. The combined aqueous phases were then concentrated on a rotary evaporator and the crude amine was isolated by filtration (ca., 44g). The analytical sample (Table 8) was obtained from ether (charcoal)-pentane.

Diethyl 6-chloro-3-pyridylaminomethylenemalonate (NP-26)

Solid 3-amino-6-chloropyridine (34.0g, 0.265 mole, NP-25) was slowly added to neat, diethyl ethoxymethylenemalonate (57.0g, 0.265 mole) at room temperature with efficient stirring. The mixture was then heated to 100° for one hour to drive off the ethanol produced in the condensation. After cooling to room temperature, a tan crystalline solid formed which was slurried with heptane and vacuum dried. The crude acrylate was thereby obtained in 91% yield (72.0g). The analytical sample (Table 8) was obtained from hot heptane (charcoal) as colorless needles. The proton spectrum for this product is reproduced in Figure 23.

Dimethyl methoxymalonate (NP-27)

In accord with the literature procedure (21), 216g of 25% sodium methoxide was diluted to 500 ml. with absolute methanol. Dimethylmalonate (114 ml.) was then added at room temperature. The suspension was then heated to 50°, and methyl formate (125 ml.) was added dropwise to the clear yellow solution. The mixture was then refluxed for six hours before cooling to room temperature. The suspension was filtered, the crude salt washed with 800 ml. of ether, and then dried under vacuum at room temperature. The crude salt (123g) was then slurried in 1ℓ of toluene at room temperature. Dimethyl sulfate (135 ml) was added, and the mixture refluxed for three hours. After cooling, the inorganic salt was removed by filtration and solvent was removed from the filtrate by means of a nitrogen purge. The residual liquid was then distilled under vacuum to afford the title precursor of analytical purity (Table 10) as a colorless liquid which slowly forms a low melting solid (35.0g, b.p., 80-95°/2.0 mm, m.p. 36-39°).

Dimethyl 6-methoxy-3-pyridylamino-methylenemalonate (NP-28)

Neat 2-methoxy-5-aminopyridine (25.0g, 0.20 mole) was added dropwise into preformed dimethyl methoxymethylenemalonate (34.8g, 0.20 mole, NP-27) at 40°. An exotherm to 75° was noted during the addition, and a solid quickly formed. The mixture was heated to 100° for one hour, cooled to room temperature, heptane added (200 ml.), and the suspension refluxed for one-half hour. After cooling, crude product was isolated as a tan solid in 96% yield (51.0g). The analytical sample (Table 10) was obtained as a fluffy, white solid from ethanol (charcoal). The proton spectrum is reproduced in Figure 36.

6-Methoxy-3-nitro-2-picoline (NP-29)

In accord with the procedure as reported in the literature (38), solid 6-chloro-3-nitro-2-picoline (15.0g, 87.1 mmole, NP-24) was added to a solution of 37g. of 25% sodium methoxide in a total of 60 ml of methanol at room temperature. The mixture was then heated to 70-75° for one hour, cooled, and poured into 500 ml. of cold water with stirring. The crude product was then obtained as a brown powder in a crude yield of 70% (10.2g) after drying at room temperature. The analytical sample (Table 16) was obtained as yellow needles from pentane (charcoal).

6-Methoxy-3-Aminopicolinic Acid (NP-30)

Solid 6-methoxy-3-acetamidopicolinic acid (6.0g, 26.1 mmole, 38) was added into 48 ml. of 2.5N sodium hydroxide at room temperature. The mixture was then heated to reflux for thirty minutes and then cooled to room temperature. Dilute sulfuric acid (25%, ca., 15 ml.) was then added until the pH was adjusted to 5-6. A suspension formed which was stirred overnight at room temperature before filtering the crude acid in a yield of 55% (2.4g, m.p. 135-137°). The analytical sample (Table 16) was obtained as a beige powder by sublimation at 100-110° (0.08 mm). The infrared spectrum for this acid is reproduced in Figure 58.

Dimethyl Quinolinate (NP-31)

In accord with the reported procedure (39), quinolinic acid (100g) was refluxed in 1.2 ℓ. of absolute methanol while a slow stream of anhydrous hydrochloric acid was bubbled through. After eight hours, the solution was cooled and the methanol removed under a nitrogen purge. One normal sodium hydroxide (800 ml.) was then added to the crude solid. The basic solution was then extracted three times with 300 ml. of ether. After drying ($MgSO_4$), the ether was removed to afford crude product as a colorless solid (32.0g, m.p. 50-52°). The analytical sample (Table 17) was obtained from diethyl ether.

Dimethyl quinolinate N-Oxide (NP-32)

As reported in the literature (40), hydrogen peroxide (18 ml.) was slowly added to dimethyl quinolinate (37.0g, NP-32) in 110 ml. of glacial acetic acid at room temperature. The mixture was then warmed to 83° for two hours, cooled, an additional 18 ml. of hydrogen peroxide added, warmed to 83° for an additional two hours, and cooled again. The solvent was then removed under a strong nitrogen purge to afford a light yellow oil. Aqueous sodium carbonate was then added until the mixture was basic to litmus paper. The suspension was then extracted three times with 100 ml. of chloroform, and the crude product was isolated as a tan solid after removal of the solvent. The pure (Table 17) N-oxide was then obtained after recrystallization from methanol (21.0g).

6-Methoxy-3-acetamido-2-picoline (NP-33)

In accord with the procedure as reported in the literature (38), 6-methoxy-3-amino-2-picoline was first prepared in the following manner. A mixture of water (200 ml), methanol (200 ml), acetic acid (4 ml), and iron powder (66g) was heated to reflux. Preformed 6-methoxy-3-nitro-2-picoline (27.2g, 0.162 mole, NP-29) was then added portionwise over a period of 45 minutes while maintaining a gentle reflux. After refluxing for an additional two hours, sodium bicarbonate (30g) was slowly added and the mixture was heated to reflux again for an additional three hours. After cooling to room temperature, the mixture was filtered and the filter cake washed with 500 ml of ethanol. Most of the solvent was then removed from the combined filtrate and washings. The residue was then extracted three times with ether (600 ml total). The ether layer was then dried ($MgSO_4$), and the solvent removed to afford crude 6-methoxy-3-amino-2-picoline as an oil (18.5g).

The crude amine was not purified at this stage, but was immediately subjected to reaction with acetic anhydride. Accordingly, a solution of the crude amine (18.5g) in 45 ml of ether was slowly added dropwise into a solution of acetic anhydride (13 ml) in 60 ml of ether at room temperature. A moderate exotherm to 35° was noted, and the suspension which formed was stirred overnight. Filtration afforded crude product as an off-white solid in high yield (19.0g, m.p., 131-132°). The analytical sample (Table 16) was obtained as a white powder by recrystallization from diethyl ether.

6-Methoxy-3-acetamidopicolinic acid (NP-34)

As reported in the literature (38), a mixture of 6-methoxy-3-acetamido-2-picoline (13.0g, 72.3 mmole, NP-33), magnesium oxide (5.0g), and anhydrous magnesium sulfate (40g) in two liters of water was slowly brought to reflux with efficient stirring. Potassium permanganate (40.0g) was then added portionwise over a period of 45 minutes. The mixture was refluxed for an additional fifteen minutes before filtering hot. The filtrate was combined with a hot water wash of the cake (500 ml) and the solvent was removed to a volume of about 500 ml on a rotary evaporator. This aqueous phase was then extracted three times with 100 ml of ether; removal of the ether afforded 1.5g of unreacted starting material. The aqueous phase was then acidified with 2N hydrochloric acid to a congo red end point (ca., 52 ml). A white suspension formed which was filtered to afford the crude acid in 30% yield (4.6g). The analytically pure acid (Table 16) was obtained by recrystallization from absolute ethanol.

Dimethyl 6-chloroquinolinate (NP-35)

As reported in the literature (40), dimethyl quinolinate N-oxide (21.5g, 0.104 mole, NP-32) was mixed with 40 ml of phosphorus oxychloride at 0°. The mixture was then slowly heated to 90° and maintained at this temperature for thirty minutes. (Note: A fairly vigorous exotherm was observed near 70°). After cooling to room temperature, the excess phosphorus oxychloride was removed under reduced pressure. The resultant oily residue

was cautiously hydrolyzed with 500 ml of water and was vigorously stirred overnight at room temperature. The mixture was then extracted several times with chloroform (400 ml). The combined chloroform layers were dried over magnesium sulfate. After removal of the solvent, the crude product was obtained as an amber oil (19g.). Analytically pure dimethyl 6-chloroquinolinate (Table 17) was obtained as a colorless oil in 71% yield by vacuum distillation (111-115°/0.20 mm). The proton spectrum for this precursor is reproduced in Figure 59.

Dimethyl 6-methoxyquinolinate (NP-36)

In accord with the reported procedure (40), a solution of dimethyl 6-chloroquinolinate (40.0g, 0.174 mole, NP-35) in 80 ml. of methanol was added dropwise into a solution of sodium methoxide (48.7g of 25% solution, 0.224 mole) in 300 ml. of methanol at room temperature. The slight exotherm was easily controlled with the aid of an external water bath. The mixture was then slowly brought to reflux and maintained at this temperature for a total of three hours. The white suspension was then filtered (celite), and the filtrate cooled to -78° for two hours. Analytically pure product was then obtained in 64% yield (25.3g, m.p.t., 62-63°) by filtration of the resultant white suspension under a nitrogen blanket. The analytical data are included in Table 17 and the proton spectrum is reproduced in Figure 60.

6-Methoxyquinolindiamide (NP-37)

Preformed dimethyl 6-methoxyquinolinate (36.0g, 0.160 mole, NP-36) was stirred with 1.2ℓ of concentrated ammonium hydroxide at room temperature. The initial white suspension gradually thinned and then became thicker after several hours. Stirring was continued for a total of four hours before the solvent was removed under a strong nitrogen stream. Crude product was then obtained as a white solid in high yield. The analytically pure diamide (Table 17) was obtained by recrystallization from ethanol. The infrared spectrum is reproduced in Figure 61. Note: we have observed that the diamide as produced via this route must be rapidly separated from the aqueous phase or conversion to the bis ammonium salt of 6-methoxyquinolinic acid will be a complicating factor. However, we have also observed that the bis-ammonium salt produced will also afford 6-methoxyquinolinimide upon heating.

6-Methoxyquinolinimide (NP-38)

A 500 ml., one neck flask containing solid 6-methoxyquinolindiamide (10.0g, 51.2 mmole, NP-37) was immersed in an oil bath at room temperature. The temperature was slowly raised to 195° at which point the evolution of ammonia was noted by pH paper. The initial white solid slowly darkened as the heating continued. After one hour at 195°, the evolution of the ammonia ceased. The flask was then cooled to afford the imide as a light tan solid in 91% yield (8.4g). The crude imide was sufficiently pure for the next step, and its infrared spectrum was identical to the analytically pure imide obtained by recrystallization from glacial acetic acid. The analytical data are included in Table 17, and the infrared spectrum is reproduced in Figure 62.

Cupric 3-amino-6-methoxypicolinate (NP-39)

Aqueous sodium hypobromite solution was first prepared by the dropwise addition of bromine (22.7g, 0.142 mole) into an ice-cold aqueous solution of sodium hydroxide (156 ml. of 2N, 0.312 mole) over a period of one and one-half hours. The temperature was maintained at 0°-3° throughout this addition, and the resultant sodium hypobromite solution was kept cold and immediately used for the next step.

The Hoffmann degradation was conducted in the following manner. Our preformed 6-methoxyquinolinimide (23.0g, 0.129 mole, NP-38) was dissolved in 390 ml. of 2N sodium hydroxide at 0°-5° with efficient stirring. The sodium hypobromite solution (prepared as described above and kept cold throughout the addition) was then added dropwise into the solution of the imide over a period of one and one-half hours. The initial dark brown solution slowly lightened and was a light amber at the end of the addition. The mixture was then slowly warmed to room temperature over a period of about one hour; a noticeable darkening occurred at this point. The solution was then slowly raised to 80°-85° and maintained at this temperature for one hour to complete the rearrangement. The resultant light amber solution was cooled to room temperature and brought to a pH of 5-6 with sulfuric acid (ca., 49 ml. of 50% solution). At this stage, the pure 3-amino-6-methoxypicolinic acid could only be isolated from this reaction mixture through the intermediacy of its copper salt as described below.

The copper salt of 3-amino-6-methoxypicolinic acid was then prepared by the dropwise addition of a solution of cupric acetate (6.0g in 150 ml. of hot water containing 6 ml. of glacial acetic acid) into the well-stirred reaction mixture at room temperature. A beige suspension immediately formed, and some froathing was noted near the end of the addition. The suspension was then filtered and the beige solid vacuum dried overnight (crude yield, 25g). An analytical sample of this copper salt was isolated by trituration with hot water and drying at 110°. The analytical data are included in Table 17, and the infrared spectrum is reproduced in Figure 63.

6-Methoxy-3-aminopicolinic Acid (NP-30, via the Hoffmann degredation route)

The crude copper salt of 6-methoxy-3-aminopicolinic acid (25.0g, NP-39) was suspended in 500 ml. of water at room temperature. Hydrogen sulfide was then bubbled through this beige suspension for a period of about 1.5 hours. (Note: some froathing occurred during this stage.) The resultant black suspension was filtered and solvent removed from the filtrate by means of a nitrogen purge to afford 6-methoxy-3-aminopicolinic acid as light beige needles in a yield of 3.1g. An additional crop of this acid was obtained by slurrying the black filter cake with 500 ml. of hot water. After filtering and removal of solvent, the second crop amounted to 5.0g.

The infrared spectrum of the crude acid thus obtained (8.1g overall yield, 37% based upon the initial imide) was identical to the acid produced via hydrolysis of 6-methoxy-3-acetamidopicolinic acid (1). Moreover, the analytical sample (see below) obtained by recrystallization from water exhibited an identical melting point (137.5-139.0°).

Anal. Calcd. for $C_7H_8N_2O_3$: C, 50.00; H, 4.79; N, 16.66

Found: C, 49.84; H, 4.89; N, 16.63

Ethyl 6-Methoxy-3-aminopicolinate (NP-40)

Absolute ethanol (15g) was slowly added into concentrated sulfuric acid (15g) at 0°. Our previously characterized 6-methoxy-3-aminopicolinic acid (6.4g, 38.0 mmole, NP-30) was then slowly added as a solid. The brown solution was warmed to room temperature at which point a light beige suspension was formed. The mixture was then slowly brought to reflux and maintained at reflux for a total of four hours. After cooling, the brown solution was slowly poured onto 75g of ice with stirring. The solution was then brought to a pH of 9 with concentrated ammonium hydroxide. The resultant beige suspension was extracted three times with 150 ml. of ether. The combined ether layers were dried over magnesium sulfate, and the solvent removed to afford the crude ester as a beige solid in 58% yield (4.3g). The analytical sample (Table 18) was obtained as yellow needles from heptane. The infrared spectrum for this precursor is reproduced in Figure 64, and the proton spectrum is shown in Figure 65.

2-Benzyloxy-5-nitropyridine (NP-41)

The title precursor was prepared as reported in the literature (7). Accordingly, sodium metal (14.0g, 0.608 mole) was slowly added to 800 ml. of benzyl alcohol with external cooling. Solid 2-chloro-5-nitropyridine (95.5g, 0.603 mole) was then slowly added to the clear solution of the alcoholate at room temperature. A slight exotherm was noted throughout this addition. The mixture was then heated to 85° and maintained at this temperature for three hours. After stirring at room temperature overnight, the suspension was filtered to afford crude product (mixed with the sodium chloride by-product) in a total yield of 141g. Very little of the product (ca., 8g) was recovered by removal of the solvent from the filtrate. The combined crude products (ca., 150g) were directly used for the next step. The title product of analytical purity (Table 1) was obtained by recrystallization from methanol.

5-Amino-2-benzyloxypyridine (NP-42)

Crude 2-benzyloxy-5-nitropyridine (55.0g, 0.238 mole, NP-41) was slowly added into a mixture of methanol (100 ml.), water (100 ml.), glacial acetic acid (4 ml.) and iron powder (80.0g) at reflux. The mixture was maintained at reflux for one day and then 150 ml. of water was added to

aid the reduction. After refluxing for an additional day, 10 ml. of 20% sodium hydroxide solution was added, and the black mixture was filtered hot. The cake was then washed successively with 300 ml. of hot water and 300 ml. of hot methanol. Solvent was then removed from the combined filtrates by means of a strong nitrogen stream. The residue was then repeatedly extracted with ether. The ether layers were combined, dried over magnesium sulfate, and the solvent removed to afford the crude amine in 52% yield (25.0g). The analytically pure amine (20.8g, Table 2) was obtained by recrystallization from ethanol-heptane.

Diethyl 6-benzyloxy-3-pyridylaminomethylenemalonate (NP-43)

Preformed 5-amino-2-benzyloxypyridine (42.6g, 0.212 mole, NP-42) was slowly added with stirring into one mole-equivalent of neat diethyl ethoxymethylenemalonate. An exotherm was noted throughout the addition and a suspension quickly formed. The mixture was then heated to 95° for one hour and the ethanol produced in the condensation was allowed to escape through a short air condenser. Upon cooling to room temperature a solid quickly formed which proved to be the crude product (72.0g). The analytically pure product (Table 3) was obtained as an off-white solid by recrystallization from heptane. The proton spectrum for this precursor is reproduced in Figure 6.

4.4 Naphthyridine Intermediates (NI-1 through NI-41)

3-Carbethoxy-4-Hydroxy-6-Alkoxy-1,5-Naphthyridines (NI-1 and NI-3 thru NI-6

The title derivatives were prepared via the thermal cyclization of the appropriate diethyl 6-alkoxy-3-pyridylaminomethylenemalonates in refluxing diethyl ether. The general procedure is illustrated below for the preparation of 3-carbethoxy-4-hydroxy-6-(p-chlorobenzyloxy)-1,5-naphthyridine (NI-6).

Recrystallized diethyl 6-p-chlorobenzyloxy-3-pyridylamino-methylene malonate (27.0g, NP-13) was slowly added as a solid to 100g of refluxing diphenyl ether. The ethanol produced in the reaction was allowed to escape through a short air condenser. After the addition was completed, the mixture was maintained at reflux for 30 minutes. The suspension was cooled to about 80°, and 150 ml. of heptane slowly added with stirring. After cooling to room temperature, the suspension was filtered to afford crude product as a light tan powder. The powder was repeatedly triturated with hot ethanol before drying at 25° (0.10 mm) for two days. The yield of analytically pure (Table 4) 3-carbethoxy-6-p-chlorobenzyloxy-4-hydroxy-1,5-naphthyridine was 54% (13.0g).

2-Carbethoxy-4-hydroxy-6-methoxy-1,5-naphthyridine (NI-2)

The title product was prepared according to the general method reported by Goldberg (5). The starting material, diethyl oxalacetate, was obtained from its commercially available sodium salt via the metathetical reaction (sulfuric acid in ether) and exhibited the physical constants reported (11). After recrystallization from ethanol (charcoal), the analytical sample of NI-2 (Table 4) melted at 234-235° (lit. m.p., 224-226°, 5).

3-Carboxy-4-hydroxy-6-alkoxy-1,5-naphthyridines (NI-7 through NI-9)

These three intermediates were prepared via saponification of the corresponding esters. The products were obtained in nearly quantitative yields, and the analytical data are included in Table 5. The specific details of the conditions used to prepare 3-carboxy-4-hydroxy-6-(2,2,2-trifluoroethoxy)-1,5-naphthyridine mono-hydrate are reported below.

A suspension of 3-carbethoxy-4-hydroxy-6-(2,2,2-trifluoroethoxy)-1,5-naphthyridine (53.0g, 0.167 mole, NI-5) in 900 ml. of 1N sodium hydroxide was heated to 95° for four hours. The resultant thin suspension was cooled to room temperature, filtered (charcoal), and acidified to congo red. The thick suspension was filtered and most of the water removed by vacuum filtration. The pasty, white solid obtained was dried in a vacuum oven at 70° for several days. The yield of crude product was 83% (42.9g). The analytical sample was obtained by repeated recrystallizations from ethanol (charcoal) and was obtained as a white solid. The analytical data (Table 5) consistently revealed the presence of a mono-hydrate.

6-Alkoxy-4-hydroxy-1,5-naphthyridines (NI-10 and NI-11)

Both of these materials were obtained in quantitative yield by thermal decarboxylation in refluxing diphenyl ether solution. Below, we have described the specific details used for the preparation of the trifluoroethoxy analog (NI-11).

Phenyl ether (100g) was heated to reflux with vigorous stirring. Solid 3-carboxy-4-hydroxy-6-(2,2,2-trifluoroethoxy)-1,5-naphthyridine monohydrate (43.0g of NI-9) was slowly added over a period of 1-2 hours. The evolution of CO_2 was evident throughout the addition. The brown solution was heated an additional ten minutes, and then cooled. At about 60°, 150 ml. of heptane was added and the suspension cooled down to room temperature. Crude product was obtained in quantitative yield by filtration. The analytical sample (Table 6) was obtained as a white powder after recrystallization from ethanol (charcoal).

6-Alkoxy-4-chloro-1,5-naphthyridines (NI-12 and NI-13)

Goldberg's general procedure was applied for the preparation of the title derivatives (5). Both were prepared by essentially the same procedure, and the specific details for the preparation of the 2,2,2-trifluoroethoxy analog are discussed below.

Solid 4-hydroxy-6-(2,2,2-trifluoroethoxy)-1,5-naphthyridine (10.0g, 0.041 mole, NI-11) was slowly added to 30g of vigorously stirring phosphorus oxychloride at room temperature. A mild exotherm to about 50° was noted at this stage. The mixture was then heated to 95° for one hour and cooled to 55°. The thick solution was then carefully hydrolyzed by slowly pouring onto 500g of ice with with vigorous stirring. After the hydrolyzed mixture warmed to room temperature, sodium acetate (ca., 130g) was added until the solution was just neutral to congo red. The dark aqueous mixture was then extracted three times with 300 ml. of ether. The ether layer was washed twice with 300 ml. of saturated sodium bicarbonate solution and dried with sodium sulfate. After removal of the ether by means of a nitrogen purge, 4-chloro-6-(2,2,2-trifluoroethoxy)-1,5-naphthyridine was obtained as an off-white, crystalline solid in a crude yield of 76% (8.2g). The analytical sample (Table 6) was obtained as colorless needles from pentane (charcoal).

2,4-Dihydroxy-1,5-naphthyridine (NI-14)

Ethyl 3-aminopicolinate (14.6g, 87.8 mmole) was slowly added as a solid into 125 ml. of diethyl malonate at 200°. After the addition was completed, the resultant brown solution was cooled to room temperature. The excess diethyl malonate was then removed via vacuum distillation. The residual reddish-brown liquid was diluted with 400 ml. of ether and allowed to stand for one hour. A small amount of brown tar was then removed by filtration. To the clear orange filtrate was added a solution of sodium ethoxide (8.7g) in 100 ml. of absolute ethanol. A suspension immediately formed which was stirred overnight at room temperature. The suspension was then refluxed for four hours and filtered to afford an off-white solid (36.0g). This solid was mixed to a paste with 30 ml. of water, and 125 ml. of 40% sodium hydroxide was added with stirring. This suspension was slowly brought to reflux to effect the decarboxylation. Considerably froathing was noted at this point, and care was required to avoid too rapid a heating rate. After the froathing had subsided, hot water was slowly added until an almost clear solution was observed (about 400 ml). The solution was filtered, and the clear orange-amber filtrate acidified to pH-4 with glacial acetic acid. The resultant light yellow suspension was filtered to afford crude 2,4-dihydroxy-1,5-naphthyridine in 97% yield (13.8g, m.p. >300°, soluble in 2N sodium carbonate). The analytical sample (Table 11) was obtained by recrystallization from a large quantity of hot water and was dried at 110° (0.10 mm).

2,4-Dichloro-1,5-naphthyridine (NI-15)

Oakes' and Rydon's procedure was used to prepare this intermediate (23). A suspension of 2,4-dihydroxy-1,5-naphthyridine (8.1g, 0.05 ml) in 97 ml. of phosphorus oxychloride was slowly heated to reflux. A brown solution formed near 80°, and a nearly black solution was present after six hours. The mixture was then cooled, and the excess phosphorus oxychloride removed by vacuum distillation. The resultant brown oil was slowly poured into 500 ml. of 10% ammonium hydroxide with vigorous stirring. After thirty minutes, crude product was isolated as a light grey solid by filtration. The yield was nearly quantitative after drying (9.7g, m.p. 140-141°). The analytical sample (Table 11) was obtained in 81% yield as a light gray solid with a heavy, musty odor by vacuum sublimation (m.p., 140-141°).

2,4-Dichloro-1,5-Naphthyridine (NI-15, via the Meisenheimer Route)

Solid 4-chloro-1,5-naphthyridine-1-N-oxide (5.0 g, 25.9 mmole, NI-39) was slowly added portionwise into 100 ml of phosphorous oxychloride at 25°. A slight exotherm to 32° was noted during this addition. The clear solution was then slowly brought to reflux and maintained at this temperature for two hours. The gray-brown solution was then cooled to room temperature and the phosphorus oxychloride removed by means of a strong nitrogen stream. The brown gum was then cautiously hydrolyzed by the addition of 150 g of ice with efficient stirring. After warming to room temperature, the off-white suspension was brought to a pH of 9-10 with concentrated ammonium hydroxide (ca., 30 ml). After filtration and drying, the title intermediate was obtained in quantitative yield (5.2 g) and exhibited spectral and physical properties identical to 2,4-dichloro-1,5-naphthyridine (NI-15) prepared according to the procedure described immediately above.

4-Chloro-2-methoxy-1,5-naphthyridine (NI-16)

As reported by McCaustland and Cheng (2), a solution of 2,4-dichloro-1,5-naphthyridine (6.5g, 32.6 mmole) in 65 ml of methanol containing 5% anhydrous hydrogen chloride was refluxed for six hours. The solvent was then removed, and the residue made alkaline by the addition of dilute ammonium hydroxide in the presence of about 30g. of ice. The grey solid obtained by filtration was triturated three times with 250 ml. of boiling heptane. The clear heptane extracts were then cooled in the refrigerator for three days, and analytically pure product (Table 13) obtained in 39% yield (2.5g, m.p., 112-113°) as small colorless needles after filtration.

4-Chloro-2-hydroxy-1,5-naphthyridine (NI-17)

In accord with the procedure as described by Oakes and Rydon (23), a mixture of 2,4-dichloro-1,5-naphthyridine (5.0g, 0.251 mole, NI-15), 60 ml. of 5 N hydrochloric acid and 45 ml of dioxane was refluxed for three hours. The mixture was then cooled and slowly poured into 500 ml. of water with stirring. Solid sodium carbonate was added until the pH was slightly alkaline (ca., 23g). A small amount of insoluble material was filtered at this point, and the filtrate was left at -5° for several days. The precipitated solid was then isolated by filtration and obtained as a grayish powder in quantitative yield (5.0g). The analytical sample (ethyl acetate, Table 13) exhibited identical spectral characteristics to the dried crude material. The infrared spectrum for this white, crystalline solid is reproduced in Figure 43.

4-Chloro-2-(2,2,2-trifluoroethoxy)-1,5-naphthyridine (NI-18)

The sodium salt of 2,2,2-trifluoroethanol was first prepared by the slow, dropwise addition of a solution of 2,2,2-trifluoroethanol (3.0g, 1.2 mole-eq.) in 50 ml. of tetrahydrofuran into a suspension of finely divided sodium metal (0.58g, 25.1 mmole) in 25 ml. of tetrahydrofuran at room temperature. This mixture was stirred overnight to insure the complete conversion into the alcoholate. The resultant slightly cloudy solution was slowly added dropwise over one hour into a suspension of preformed 2,4-dichloro-1,5-naphthyridine (5.0g, 25.1 mmole, NI-15) in 150 ml. of dry tetrahydrofuran at room temperature. A slight exotherm was noted (ca., 3-4°), however no visible change could be observed. The suspension was then slowly heated to reflux and maintained at reflux for a period of four hours. The suspension was then cooled and filtered to remove the inorganic by-product (ca., 1.2g). Solvent was removed from the colorless filtrate to afford crude product as a white solid in quantitative yield (7.0g). This solid was then dissolved in 400 ml. of boiling heptane. The solution was treated with magnesium sulfate and filtered hot. After cooling to room temperature a crystalline precipitate immediately separated from solution. The title product of analytical purity (Table 13) was thereby obtained as colorless crystals in an overall yield of 71% (4.7g, m.p., 153.0-153.5°). An additional 1.5g of product of nearly identical purity could be obtained by evaporation of the heptane solution to dryness. The proton spectrum for this derivative is reproduced in Figure 45.

4-Chloro-2-(p-chlorobenzyloxy)-1,5-naphthyridine (NI-19)

Solid p-chlorobenzyl alcohol (1.78g, 12.5 mmole) was slowly added as a solid into a suspension of solid sodium ethoxide (0.90g, 13.1 mmole) in 200 ml. of dry tetrahydrofuran at room temperature. No exotherm or visible sign of reaction was evident at this point. The suspension was then heated to 50-55° for one-half hour to complete the metathetical reaction.

After cooling to room temperature, preformed 2,4-dichloro-1,5-naphthyridine (2.5g, 12.5 mmole, NI-15) was added portionwise over two minutes. The suspension was then heated to reflux, and a perceptible lightening of the suspension color was observed. After refluxing for four hours, the mixture was cooled, and the inorganic salts removed by filtration. Solvent was removed from the clear, light amber filtrate to afford an off-white, somewhat gummy solid. This solid was then triturated with 150 ml. of boiling heptane for five minutes. The heptane layer was separated by filtration, treated with decolorizing charcoal, and filtered while hot. Upon cooling to room temperature, 4-chloro-2-(p-chlorobenzyloxy)-1,5-naphthyridine quickly separated from solution in the form of pale-pinkish, small needles (0.7g). The residue from the first heptane trituration was again extracted with 150 ml. of boiling heptane, and the heptane layer worked-up as described before. The yield of product from this second trituration proved to be 0.3 g. Both of these crops were combined to afford analytically pure product (Table 13) in an overall yield of 26% (1.0g). The proton spectrum for the analytically pure solid is reproduced in Figure 47.

3-Carbethoxy-6-ethoxy-4-hydroxy-1,5-naphthyridine (NI-20)

Diphenyl ether (300g) was heated to reflux and recrystallized diethyl 6-ethoxy-3-pyridylaminomethylenemalonate (66.7g, 0.216 mole, NP-19) was slowly added protionwise over a period of about two hours. The ethanol produced in the reaction was allowed to escape through a short air condenser. After the addition was completed, the mixture was refluxed an additional 15 minutes before cooling to room temperature. Heptane (450 ml) was added and the resultant suspension filtered to afford the crude product as a brown solid in 85% yield (48.0g). The analytical sample (Table 4) was obtained by repeatedly triturating the crude ester with hot ethanol.

3-Carboxy-6-ethoxy-4-hydroxy-1,5-naphthyridine hemi-hydrate (NI-21)

Preformed 3-carbethoxy-6-ethoxy-4-hydroxy-1,5-naphthyridine (45.0g, 0.172 mole, NI-20) was quickly added to 900 ml. of normal sodium hydroxide at room temperature. The suspension was heated with stirring to 100°. The suspension slowly cleared, and the heating was continued overnight. The clear, dark solution was then cooled to room temperature and filtered to remove a small amount of insoluble solids. The filtrate was then titrated to a congo red end point with concentrated hydrochloric acid (ca., 135 ml.). The dark suspension was filtered and the crude acid was thereby isolated as a brown solid (22g). An infrared spectrum of the crude acid clearly exhibited numerous impurity peaks. The crude acid was therefore taken up in 900 ml. of 1 N sodium hydroxide and reprecipitated with concentrated hydrochloric acid. After drying, the acid was obtained as a light brown powder in a crude yield of 32% (13.0g). An infrared spectrum again disclosed the presence of impurities, however, they were reduced in intensity. The analytical sample (Table 5) was obtained by recrystallization from ethanol (charcoal)-pentane.

3-Carboxy-6-(p-chlorobenzyloxy)-4-hydroxy-1,5-naphthyridine (NI-22)

Preformed 3-carbethoxy-6-(p-chlorobenzyloxy)-4-hydroxy-1,5-naphthyridine (11.0g, 30.7 mmole, NI-6) was added to 200 ml. of 1 N sodium hydroxide and was refluxed overnight. After cooling, a suspension formed which was neutralized to congo red by the addition of concentrated hydrochloric acid (ca., 18 ml.). The resultant white suspension was filtered, and the filter cake washed repeatedly with water before drying at 110° (0.10 mm). The crude product was thereby obtained as a white powder in quantitative yield. The analytical sample was obtained by redissolving the crude acid in dilute (1N) sodium hydroxide and acidifying whith warm hydrochloric acid to a congo red end point. After washing repeatedly with water and drying at 110° (0.10 mm), the analytically pure acid (Table 5) was obtained as a white powder in moderate yield.

4,6-Dichloro-1,5-naphthyridine (NI-23)

Crude 6-(p-chlorobenzyloxy)-4-hydroxy-1,5-naphthyridine (46.0g, 0.161 mole) was heated to reflux with 150 ml. of phosphorus oxychloride for three hours. The resultant black mixture was cautiously hydrolyzed by adding into 1,500g of ice with vigorous stirring. After warming to room temperature, sodium acetate was added to the congo red end point (ca., 900g). The aqueous phase was then filtered to remove an insoluble portion (14g), and the clear, brown filtrate was extracted with ca., 2.5ℓ of ether. The ether layer was then washed three times with 1.5ℓ of saturated sodium bicarbonate solution, dried over magnesium sulfate, and the solvent removed under a nitrogen purge. The residual solid was isolated in very low yield (4.0g, 12%) after removal of the ether. This solid was recrystallized from ether (charcoal) at -70° and was isolated as small white needles (2.1g). The analytical data for this solid (Table 8) are in agreement with the formulated structure. The proton spectrum (Figure 27) again, is in complete agreement with the proposed structure.

4-Amino-6-n-butoxy-1,5-naphthyridine (NI-24)

In accord with the reported procedure (5), solid potassium hydroxide (3.0g) was dissolved in phenol (25g) at 90°. Preformed 6-n-butoxy-4-chloro-1,5-naphthyridine (13.1g, 55.4 mmole, NI-12) was then added as a solid at 90°, and the mixture subsequently heated to 160° for three hours. After cooling, the mixture was poured into 500 ml. of 2 N sodium hydroxide. The organic phase was extracted with ether (3 x 150 ml.), washed twice with dilute sodium hydroxide, once with water and finally dried over magnesium sulfate. After removal of the ether, the crude 6-n-butoxy-4-phenoxy-1,5-naphthyridine was obtained as an oil in a crude yield of 15g. This oil was mixed with 75g of ammonium acetate, heated to 140°, and anhydrous ammonia bubbled through for a total of five hours. The mixture was then cooled, mixed with water (150 ml.), filtered (charcoal), and the filtrate made basic with ammonium hydroxide (80 ml.). The crude product separated from solution

as an oil and was isolated by means of a separatory funnel. This oil would not crystallize even when cooled and scratched. Consequently, the oil was repeatedly triturated with hot heptane. The combined heptane layers were treated with charcoal, magnesium sulfate, and the clear filtrate was allowed to stand at 0° for several days. The title product of analytical purity (Table 7) separated from solution as a white, micro-crystalline solid and was isolated in moderate yield. The proton spectrum for this intermediate is reproduced in Figure 22.

3-Carbethoxy-6-chloro-4-hydroxy-1,5-naphthyridine (NI-25) and 3-Carbethoxy-4,6-dihydroxy-1,5-naphthyridine (NI-26)

Diethyl 6-chloro-3-pyridylaminomethylenemalonate (36.0g, 0.120 mole, NP-26) was slowly added as a solid into 150g of refluxing (248°) diphenyl ether with efficient stirring. The evolution of ethanol was readily apparent and considerable froathing occurred. After the addition was completed, heating was immediately discontinued and the mixture cooled. At 80°, 200 ml of heptane was added and the suspension was cooled to room temperature. The crude tan solid was then isolated by filtration and weighed 26g. This crude solid proved to be a mixture which contained at least three components. This was verified in the following manner. The crude product (5.0g) was triturated at the boiling point with 200 ml of absolute ethanol. Filtration of the hot ethanol suspension afforded the 6-chloro ester (2.0g, NI-25) as a dark gray highly insoluble solid. The analytical data for this ester are included in Table 8, and its infrared spectrum is reproduced in Figure 24. The clear and dark ethanol filtrate was then treated with charcoal and refiltered while hot. After cooling to room temperature, a dark tan solid slowly precipitated. To date, this material has eluded all attempts to complete its characterization. The filtrate from this step was then diluted with one volume of ether and cooled to -20° overnight. The precipitated solid (1.5g) exhibited an infrared spectrum (Figure 25) identical to the recrystallized analytical sample of the 6-hydroxy ester (ethanol-pentane, NI-26). The analytical data for NI-26 are included in Table 8.

3-Carboxy-6-chloro-4-hydroxy-1,5-naphthyridine (NI-27)

A suspension of 3-carbethoxy-6-chloro-4-hydroxy-1,5-naphthyridine (6.4g, 25.3 mmole, NI-25) in 120 ml. of 1N sodium hydroxide was heated to reflux. A clear solution was present at 80°, and the solution was refluxed for a total of 45 minutes before immediately cooling to room temperature. A suspension of the sodium salt of the acid formed at room temperature. The sodium salt was removed by filtration, resuspended in about 120 ml. of water, and neutralized to a congo red end point with concentrated hydrochloric acid (ca., 6 ml.). The suspension was then filtered to afford the title product as a tan powder in high yield after drying at 110°. The analytical data are included in Table 8, and the infrared spectrum is reproduced in Figure 26.

A preliminary decarboxylation experiment performed upon this acid revealed that temperatures greater than refluxing diphenyl ether (250°) are required, since absorptions in the carbonyl region were still present. Moreover, reaction of this crude product with phosphorus oxychloride via our usual technique afforded less than 10% of our previously characterized 4,6-dichloro-1,5-naphthyridine (NI-23).

4-Chloro-6-methoxy-1,5-naphthyridine (NI-28)

Previously characterized 4,6-dichloro-1,5-naphthyridine (7.0g, 35.1 mmole, NI-23) was added portionwise as a solid to a solution of sodium methoxide (7.59g of 25% solution, 35.1 mmole) in 135 ml. of methanol at room temperature. The mixture was slowly heated, and a clear solution was present near 40-50°. A suspension formed as the reflux began, and the mixture was maintained at reflux for 24 hours. Solvent was then removed under a nitrogen purge to afford crude product (and sodium chloride) as a white solid. This mixture was then sublimed at 80-100° (0.04 mm) to afford analytically pure product as a white solid in 88% yield (6.0g, m.p. 93-94°). The analytical data are included in Table 8, and the proton spectrum is reproduced in Figure 28.

4-Chloro-6-ethoxy-1,5-naphthyridine (NI-29)

Our previously characterized 3-carboxy-4-hydroxy-6-ethoxy-1,5-naphthyridine (NI-21) was first decarboxylated in refluxing diphenyl ether in accord with our standard technique. Full decarboxylation was not observed since carbonyl absorptions were still present near 5.9μ. Also, all attempts to separate the pure 6-ethoxy-4-hydroxy-1,5-naphthyridine were unsuccessful since the product(s) was highly insoluble. Accordingly, the crude 6-ethoxy-4-hydroxy-1,5-naphthyridine (14.0g) was slowly added to 50 ml. of phosphorus oxychloride at room temperature. The suspension was then heated to reflux and maintained there for an additional hour before cooling the dark suspension to room temperature. The mixture was carefully hydrolyzed on 1500g of ice with vigorous stirring. Solid sodium acetate was then slowly added (ca. 280g) until the mixture was neutral to congo red. This mixture was then repeatedly extracted with ether until no further color was removed into the extracts. All of the ether layers were then combined and washed well with a saturated aqueous sodium bicarbonate solution until no further effervescence was observed. The ether phase was then dried over magnesium sulfate and the solvent removed under a nitrogen purge. At this stage, a crystalline solid was obtained in a yield of 6.0g. A proton spectrum ($CDCl_3$) of this solid proved it to be a 50:50 mixture of the title 4-chloro-6-ethoxy-1,5-naphthyridine (NI-29) and our previously characterized 4,6-dichloro-1,5-naphthyridine (NI-23). The run as described above was repeated to afford an additional 6.0g of white solid with identical spectral characteristics. The crude mixture (10.5g) was dissolved in 1.2 l. of hot heptane, treated with charcoal and magnesium sulfate, filtered while hot, and cooled to -20° for two hours. The crystals which separated were filtered and proved to be pure 4,6-dichloro-1,5-naphthyridine (2.1g, NI-23) by comparison with a known sample (I.R., mixed m.pt.). The solvent was removed from

the heptane filtrate to afford crude 4-chloro-6-ethoxy-1,5-naphthyridine as a white solid in a yield of 4.3g. Analytically pure 4-chloro-6-ethoxy-1,5-naphthyridine (NI-29) was obtained as a white solid in an essentially quantitative sublimation (65°, 0.03 mm). The analytical data for this product are included in Table 8, and the proton spectrum is reproduced in Figure 29. This same product (I.R., mixed m.p.) was obtained in virtually quantitative yield by the reaction of one mole-equivalent of sodium ethoxide with 4,6-dichloro-1,5-naphthyridine (NI-23) in refluxing ethanol solution.

2,4-Di-(5-isopropylaminopentylamino)-1,5-naphthyridine (NI-30); Attempted formation of 2-(2,2,2-trifluoroethoxy)-4-(5-isopropylaminopentylamino)-1,5-naphthyridine

A mixture of our previously characterized 2-(2,2,2-trifluoroethoxy)-4-chloro-1,5-naphthyridine (3.0g, 11.4 mmole, NI-18), potassium carbonate (2.1g, 15.2 mmole) and 5-isopropylaminopentylamine (10.0g, 69.5 mmole) was slowly raised to 170° and maintained at this temperature for a total of eighteen hours. The amber suspension was then cooled, 50 ml. of ether added, and the inorganic salt removed by filtration. The filtrate was shaken well with 50 ml. of 5N sodium hydroxide, and the ether layer was combined with two succeeding ether extracts (ca., 75 ml.) of the water layer. The ether extracts were combined, dried with magnesium sulfate and the solvent finally removed to afford an amber liquid. When subjected to molecular distillation, most of the diamine was collected over the range 25-100° (0.20 mm). Very little else distilled until a bath temperature of 190° was reached. A yellow-amber oil was then collected fairly quickly over the range 190-195° (0.05 mm); yield, 3.2g, 67%, n_D^{25} 1.5628. Analytical data (Table 15) and the proton spectrum (Figure 53) were solely consistent with the structure as formulated for NI-30.

2,4-Di-(5-isopropylaminopentylamino)-1,5-naphthyridine di-β-resorcylate mono-hydrate (NI-31)

An excess of 2,4-dihydroxybenzoic acid (2.51g, 16.3 mmole) in about 100 ml. of ether was added dropwise into a solution of 2,4-di-(5-isopropylaminopentylamino)-1,5-naphthyridine (1.5g, 3.62 mmole, NI-30) in about 200 ml. of ether at room temperature. A thick, white suspension quickly formed, and more ether was added during the reaction to keep the mixture fluid. After stirring for several hours, the suspension was filtered to afford the title salt as a white powder (2.2g, 82%, m.p. 106-109°). The analytical data are included in Table 15 and are consistant with a di-β-resorcylate, mono-hydrate salt.

2,4-Di-(4-diethylamino-1-methylbutylamino)-1,5-naphthyridine (NI-32)

A mixture of 2,4-dichloro-1,5-naphthyridine (4.0g, 20.1 mmole, NI-15), 2-amino-5-diethylaminopentane (25.0g, 0.157 mole) and a catalytic

quantity of copper-bronze (0.5g) was heated to 180° for 18 hours. The resultant brown suspension was shaken with 50 ml. of 5N sodium hydroxide. The organic phase was separated and combined with three, 75 ml. ether extracts of the aqueous phase. The combined ether layers were dried over magnesium sulfate and filtered. Both the ether and excess diamine were then removed from the filtrate by a strong nitrogen stream for about two days. The resultant thick brown gum was then subjected to molecular distillation. Very little distillate was collected over the range 25-180° (0.035 mm). The title product was then isolated as a yellow-amber oil in 56% yield (5.0g, 190-195°/0.035 mm). The analytical data for NI-32 are included in Table 15 and its proton spectrum is reproduced in Figure 54.

2,4-Di-(4-diethylamino-1-methylbutylamino)-1,5-naphthyridine tri-β-resorcylate mono-hydrate (NI-33)

A solution of 2,4-dihydroxybenzoic acid (4.22g, 27.5 mmole, 4.5 mole-eq.) in 150 ml. of ether was added dropwise into a solution of 2,4-di-(4-diethylamino-1-methylbutylamino)-1,5-naphthyridine (2.70g, 6.10 mmole, NI-32) in 350 ml. of ether at 25°. The white suspension was stirred for several hours and then filtered to afford the title product in 85% yield (4.8g, m.p., 108-111°). The analytical data (Table 15) for both this material and a duplicate preparation were virtually identical, and were solely consistant with the empirical formula formulated for NI-33.

2-Methoxy-4-phenoxy-1,5-naphthyridine (NI-34)

Preformed 4-chloro-2-methoxy-1,5-naphthyridine (2.9g, 14.9 mmole, NI-16) was slowly added as a solid into a mixture of phenol (10g) and potassium hydroxide (1.0g) at 90°. The mixture was then heated to 160° for three hours and cooled to room temperature. The mixture was then slowly poured into 200 ml. of 2N sodium hydroxide. This solution was then extracted three times with 100 ml. of ether. The combined ether layers were washed twice with dilute sodium hydroxide, once with 200 ml. of water, dried over magnesium sulfate, and the solvent removed to afford 2.4g of the crude 4-phenoxy compound as an oil. The crude phenoxy derivative was then added to 30g of ammonium acetate, heated to 130° with stirring, and anhydrous ammonia bubbled through for two hours. After cooling to room temperature, water (75 ml.) and glacial acetic acid (5 ml.) was added, and the mixture charcoal filtered. The pH was then adjusted to 8 with ca., 16 ml. of ammonium hydroxide, and the mixture stirred for several hours until a gummy solid formed (1.0g). This solid was recrystallized from ether-pentane to afford the unreacted 2-methoxy-4-phenoxy-1,5-naphthyridine as a white solid (0.7g). The analytical data are included in Table 15, and the infrared spectrum is reproduced in Figure 55.

4-Amino-6-n-butoxy-1,5-naphthyridine hydrochloride (NI-35)

A mixture of 4-amino-6-n-butoxy-1,5-naphthyridine (3.7g, 17.0 mmole, NI-24) and 4-bromo-1-phthalimidopentane (2.6g, 8.4 mmole) was heated to reflux at 140-145° for eighteen hours. Note: The 4-bromo-1-phthalimidopentane was prepared as Chu had described (16) and was isolated as a colorless oil by molecular distillation (125°/0.08 mm; theory for $C_{13}H_{14}BrNO_2$: C, 52.72; H, 4.76; N, 4.73. Found: C, 53.04; H, 4.68; N, 4.78). The resultant amber oil was cooled and 50 ml. of benzene added. The suspension which formed was filtered, and solvent was removed from the filtrate to give an orange-amber gum. This gum was refluxed for six hours with 25 ml. of ethanol containing 0.43 g. of hydrazine hydrate. The mixture was then made acidic to congo red with 8N hydrochloric acid. The suspension was filtered, and the filtrate and hot water wash of the cake were combined. The ethanol was removed by a nitrogen purge and the aqueous solution was then made strongly basic with dilute sodium hydroxide solution. Several ether extracts of the water layer were then combined and the solvent removed to afford a tan crystalline solid. This solid was dissolved in ca., 100 ml. of ether (charcoal) and anhydrous hydrogen chloride bubbled through. The white suspension was filtered and, after drying at 80°, a tan powder was obtained in about 1g. yield. This material proved to be the hydrochloride salt of the starting material and not of the primaquine side-chain analog. This was verified by elemental analysis (Table 7) and comparison of the infrared spectrum with authentic hydrochloride prepared in ether.

6-Methoxy-2,4-dihydroxy-1,5-naphthyridine (NI-36)

Solid ethyl 6-methoxy-3-aminopicolinate (3.0g, 153.3 mmole, NP-40) was slowly added portionwise over a period of about fifteen minutes into neat diethyl malonate (50 ml.) at 195-200°C. The mixture was maintained at this temperature for an additional one-half hour to complete the condensation. The resultant red-brown solution was cooled to room temperature and the excess diethyl malonate removed via vacuum distillation. The residual reddish-brown semi-solid was taken up in 200 ml. of ether and filtered to remove a small amount of insoluble solid (ca., 0.05g). To the well-stirred ether filtrate at room temperature, a solution of sodium ethoxide (1.56g, 23.0 mmole) in about 25 ml. of ethanol was slowly added dropwise over a period of one and one-half hours. A brown suspension formed which slowly lightened in color throughout the addition. After stirring at room temperature overnight, the suspension was refluxed for four hours and then filtered to afford a light tan solid (6.2g). This solid was suspended in a mixture of 20 ml. of water and 20 ml. of 50% sodium hydroxide solution. The suspension was then slowly heated to 100°. A clear amber solution formed after five minutes which was kept at 100° for a total of thirty minutes. After adding 75 ml. of hot water, the solution was filtered hot to avoid the separation of the moderately soluble sodium salt. The filtrate was maintained at 40-50°, and glacial acetic acid was added to obtain a pH of 5-6. The resultant white suspension was cooled to 10° and filtered to afford the crude dihydroxy compound as a white solid in 51% yield (1.5g, m.p., 285-290°). The infrared spectrum for this derivative is reproduced in Figure 66. An analytical sample (Table 18) was obtained by triturating with warm water and drying under reduced pressure.

2,4-Dichloro-6-methoxy-1,5-naphthyridine (NI-37)

Preformed 6-methoxy-2,4-dihydroxy-1,5-naphthyridine (4.7g, 24.4 mmole, NI-36) was slowly added to neat phosphorus oxychloride (100 ml.) at 25°. A moderate exotherm to 32° was noted during this addition. The suspension was then slowly brought to reflux. A clear amber solution formed near 50°, and a slight froathing (HCl) was noted near 80-85°. After refluxing for 4.5 hours, the dark amber solution was cooled to room temperature and stirred overnight. The excess phosphorus oxychloride was removed under reduced pressure to afford a greyish-tan semi-solid. This residue was cautiously hydrolyzed by adding 150g of ice at 0-5° with efficient stirring. After warming to room temperature, concentrated ammonium hydroxide was added to the white suspension until the mixture was definitely basic (pH 9-10). Crude product was then obtained as a white powder in 80% yield (3.8g, m.pt., 138-140°) by filtration. The analytical sample (Table 18) was obtained as a fluffy white solid by recrystallization from heptane. The proton spectrum for this intermediate is reproduced in Figure 67.

4-Chloro-1,5-naphthyridine (NI-38)

As reported in the literature (31), a mixture of 4-hydroxy-1,5-naphthyridine (28.0g, 0.192 mole) and phosphorus oxychloride (500 ml.) was slowly brought to 100° and maintained at that temperature for three hours. The dark mixture was then cooled and the excess phosphorus oxychloride removed under reduced pressure. The residue was then cautiously hydrolized with 600 ml. of ice water with efficient stirring. The suspension was then filtered to remove some black solid, and the filtrate was brought to a pH of 7 with con. ammonium hydroxide (ca., 45 ml.). Solvent was then removed from the neutralized solution by means of a strong nitrogen stream. The residue was then extracted twice with 300 ml. of hot benzene. The benzene layer was then dried (magnesium sulfate), and the solvent removed to afford crude product as a yellow-tan solid in 30% yield (9.5g, m.p., 101-103°). The analytical sample (Table 12) was obtained as a colorless solid by recrystallization from heptane and subliming at 80° (0.10 mm). The proton spectrum for this intermediate is reproduced in Figure 41.

4-Chloro-1,5-Naphthyridine-1-N-oxide (NI-39)

A solution of m-chloroperoxybenzoic acid (24.3 mmole, 4.94g of 85% pure material) in 200 ml. of chloroform was slowly added dropwise over a period of about two hours into a solution of 4-chloro-1,5-naphthyridine (2.0g, 12.2 mmole, NI-38) in 250 ml. of chloroform at 25°. No exotherm or visible sign of reaction was noted during this addition. After stirring at room temperature for two days, the chloroform solution was washed with aqueous potassium carbonate (35g in 500 ml. of water). After a second potassium carbonate wash (17g in 250 ml. water), the chloroform layer was dried (magnesium sulfate) and then concentrated to about 50 ml. under a nitrogen purge. The addition of 250 ml. of heptane immediately produced a suspension. Crude product was obtained as a yellow-tan solid in 64% yield by filtration (1.5g). The analytical sample (Table 12) was obtained from chloroform-heptane and its proton spectrum is reproduced in Figure 42.

2-Benzyloxy-4-chloro-1,5-naphthyridine (NI-40)

Benzyl alcohol (2.70g, 25.4 mmole) was slowly added into a well stirred mixture of sodium metal (0.58g, 25.1 mmole) in 500 ml. of tetrahydrofuran at room temperature. An additional quantity of the alcohol (8.10g, 76.2 mmole) was added over two days and the mixture was refluxed for an additional day to complete the formation of the alcoholate. Solid 2,4-dichloro-1,5-naphthyridine (4.98g, 25.0 mmole, NI-15) was then added at room temperature and the mixture was refluxed for one day. The suspension was then filtered and the solvent removed from the filtrate to afford an off-white solid. This solid was taken up in one liter of hot heptane, treated with magnesium sulfate-charcoal, and filtered while hot. The title intermediate of analytical purity (Table 13) separated from solution and was isolated as a white solid in 35% yield (2.4g, m.pt. 139-140°). The proton spectrum for this compound is reproduced in Figure 46.

3-Carbethoxy-4-hydroxy-6-benzyloxy-1,5-naphthyridine (NI-41)

Recrystallized diethyl 6-benzyloxy-3-pyridylaminomethylenemalonate (52.4g, 0.141 mole, NP-43) was slowly added into 500 ml. of phenyl ether at reflux (250°C) over a period of ca., 1.5 hours. The mixture was maintained at reflux for an additional fifteen minutes before cooling to room temperature. Heptane was added (ca., 500 ml.) and the suspension filtered to afford the crude ester. This crude ester was slurried with hot heptane and filtered to remove the adherent phenyl ether. The total yield of the crude ester was ca., 80% (37g.). The analytical sample (Table 4) was obtained as a pale tan powder by trituration with hot ethanol.

4.5 Naphthyridine Targets (NT-1 through NT-19)

6-n-Butoxy-4-(4-diethylamino-1-methylbutylamino)-1,5-naphthyridine (NT-1)

In accord with Goldberg's report (5), a mixture of 6-n-butoxy-4-chloro-1,5-naphthyridine (3.0g, 12.7 mole, NI-12), 4-diethylamino-1-methylbutylamine (10.2g) and copper-bronze (0.5g) was slowly heated to 180-190°. The mixture was maintained at 180-190° for eighteen hours with vigorous stirring. The resultant brown solution was cooled to room temperature, and 50 ml. of 5N sodium hydroxide solution slowly added to neutralize the hydrochloric acid generated in the reaction. The upper, brown oily phase was extracted into ether and the ether layer dried with magnesium sulfate. After removal of the ether, the residual brown oil was subjected to molecular distillation. The excess diamine was slowly removed over a range of 25-150° (0.08 mm). The product was then isolated by a slow, controlled molecular distillation at 150-190° (0.10 mm). Most of the product distilled over the range of 160-170° (0.10 mm) and was isolated as an orangish-yellow oil in an overall yield of 82% (3.6g). The analytical data are included in Table 1, and the proton spectrum exhibited

the predicted appearance. This product eluded all attempts to prepare an isolable hydrochloride, phosphate, sulfate or citrate derivative. For characterization purposes, the dipicrate (5) was prepared in ethanol, and agreed with the formulated structure. The analytical data for this dipicrate salt are also included in Table 1.

6-(2,2,2-Trifluoroethoxy)-4-(4-diethylamino-1-methylbutylamino)-1,5-naphthyridine (NT-2)

Preformed 4-chloro-6-(2,2,2-trifluoroethoxy)-1,5-naphthyridine (3.0g of NI-13), 4-diethylamino-1-methylbutylamine (11.0g) and a catalytic quantity of copper-bronze (0.5g) was slowly heated to 180-190° and maintained at that temperature for a total of eighteen hours. After cooling, 50 ml. of 5 N sodium hydroxide was added and the mixture was extracted three times with ether. The ether layer was dried over magnesium sulfate and the solvent removed under a nitrogen purge. The residual brown oil was subjected to molecular distillation. Crude product was isolated in 91% yield (4.0g, 120-165°/0.04 mm). Analytically pure product (Table 1) was obtained as a yellow oil in 55% yield (2.4g) by a repeated molecular distillation (120-140°/0.06 mm). The proton spectrum is reproduced in Figure 17, and the following assignments have been made. NMR ($CDCl_3$): 1.57τ (1H, d, ring H-2); 1.88τ (1H, d, ring H-8); 2.95τ (1H, d, ring H-7); 3.49τ (1H, d, ring H-3); 4.02τ (1H, d, N-H, d, ring H-3); 4.02τ (1H, d, N-H, $J_{N-H, C-H}$ = 8.1 H_2); 5.15τ (2H, q, CF_3-CH_2-O, J_{HF} = 8.4 H_z); 6.30τ (1H, broad m, C-H); 7.51τ (6H, q, $N-CH_2-$); 8.2-9.2τ (13H, m, side chain-CH_2-, CH_3); $J_{2.3}$ = 5.1 Hz; and $J_{7.8}$ = 9.0 Hz.

A dipicrate was prepared for characterization purposes and was recrystallized from ethanol. The analytical data for this salt are also included in Table 1.

6-n-Butoxy-4-(5-isopropylaminopentylamino)-1,5-naphthyridine (NT-3)

A mixture of 6-n-butoxy-4-chloro-1,5-naphthyridine (3.0g, 6.33 mmole of NI-12), 5-isopropylaminopentylamine (10.0g,13) and a catalytic quantity of copper-bronze (0.5g) was slowly heated to 180-190° and maintained at this temperature for a total of eighteen hours. After cooling to room temperature, 50 ml of 5 N sodium hydroxide was slowly added with vigorous stirring. The upper brown oily phase was extracted into ether, and the ether layer dried over magnesium sulfate. After removal of solvent, the residual brown liquid was subjected to molecular distillation. Analytically pure product (Table 1) was obtained as a yellow oil in 50% yield (2.2g, 175-185°/0.15 mm). The proton spectrum is reproduced in Figure 19, and the assignments are discussed in the text of this report.

2-Methoxy-4-(5-isopropylaminopentylamino)-
1,5-naphthyridine (NT-4)

Recrystallized 4-chloro-2-methoxy-1,5-naphthyridine (3.0g, 15.4 mmole, NI-16), one equivalent of potassium carbonate (2.1g), and an excess of 5-isopropylaminopentylamine (10.0g,13) were mixed in a one-neck flask at room temperature. The suspension was slowly heated to 170° and maintained at this temperature for eighteen hours with the aid of an external oil bath. The mixture was then cooled to 25°, and 50 ml of ether added to the medium amber suspension. The inorganic salt was removed by filtration, and 50 ml. of 5 N sodium hydroxide solution was added to the ether solution with vigorous stirring. The ether layer was then separated and combined with the two 50 ml. ether extracts of the water layer. After drying over magnesium sulfate, solvent was removed from the ether layer to afford a medium brown liquid. This residual liquid was then subjected to molecular distillation. The excess diamine was removed over the range of 90°-130° (0.08 mm). The title product was subsequently obtained as a yellow oil in two cuts. The first cut (2.0g) distilled over the range 155-160° (0.04 mm) and exhibited identical spectral characteristics to that of the second cut. Analytically pure product (Table 14)was obtained as a yellow oil in 54% yield (160-170°/ 0.04 mm, 2.5g, n_D^{23} 1.5663). The proton spectrum for this material is reproduced in Figure 48.

2-Methoxy-4-(5-isopropylaminopentylamino)-
1,5-naphthyridine β-resorcylate (NT-5)

A solution of 2,4-dihydroxybenzoic acid (2.60g, 16.9 mmole, 2.9 mole-eq.) in 42 ml. of diethyl ether was slowly added dropwise into the solution of preformed 2-methoxy-4-(5-isopropylaminopentylamino)-1,5-naphthyridine (1.76g, 5.83 mmole, NT-4) at room temperature. A very pale yellowish suspension immediately formed as the addition was started. After the addition was completed, the suspension was stirred an additional three hours at room temperature. The suspension was then filtered under a nitrogen atmosphere and immediately dried in a vacuum oven at room temperature. The title product was isolated as an off-white powder in a crude yield of 94% (2.50g, m.p., 167-168°). The analytical data are included in Table 14,and the infrared spectrum is reproduced in Figure 49.

2-Hydroxy-4-(4-diethylamino-1-methylbutylamino)-
1,5-naphthyridine (NT-6)

Previously recrystallized 4-chloro-2-hydroxy-1,5-naphthyridine (2.5g, 13.8 mmole, NI-17), 2-amino-5-diethylaminopentane (20g), and a catalytic quantity of copper-bronze (0.5g) were mixed well at room temperature. This suspension was then slowly heated to a temperature of 180° and maintained there for a total of eighteen hours with the aid of an external oil bath. After cooling to room temperature, 60 ml. of 5 N sodium hydroxide was quickly added into the brown solution with efficient stirring. The upper, oily phase was separated and combined with several ether extracts of the water layer. The organic layer was then dried ($MgSO_4$), and the ether removed by means of a nitrogen purge. The residual brown oil was then fractionated through a molecular distillation apparatus. Excess diamine was first removed as a colorless liquid (ca., 60-135°/0.04 mm). Very little

distillate was next ovtained over the range 135-190° (0.02 mm). The title product distilled very slowly over a period of twenty-four hours and was collected as an amber gum in 84% yield (3.5g, 190-195°/0.02 mm). The analytical sample (Table 14)was obtained by recrystallization from ether (charcoal)-pentane and was obtained as a white powder (1.9g, m.pt. 95-96°). The infrared and proton spectra (Figures 50 and 51, respectively) for the recrystallized material were identical to the gum obtained by molecular distillation.

2-Hydroxy-4-(5-isopropylaminopentylamino)-1,5-naphthyridine (NT-7)

Previously recrystallized 4-chloro-2-hydroxy-1,5-naphthyridine (2.5g, 13.8 mmole, NI-17) was quickly added into a suspension of copper-bronze (0.5g) and 5-isopropylaminoamylamine (10.0g, 69.5 mmoles, 13) at room temperature. The suspension was then slowly heated with stirring by means of an external oil bath. A brown solution formed near 120°. The mixture was then maintained at 180° for a total of eighteen hours before cooling to room temperature. A 5 N solution of sodium hydroxide (50 ml.) was then added with efficient stirring to neutralize the hydrochloric acid produced in the reaction. At this stage, the organic phase was present as a brown oil on top of the water layer. In accord with our previous technique, 200 ml. of ether was then added to pick up the organic layer. However, the addition of the ether immediately precipitated a tan solid from the upper organic phase. An additional 100 ml. of ether was added with stirring, and the three phase system (water, ether and solid) was filtered to afford a tan, somewhat gummy solid. The solid was taken-up in 150 ml. of hot tetrahydrofuran, treated with charcoal and filtered. The resultant clear amber solution was dried with magnesium sulfate and filtered again. An excess of dry ether (ca., 300 ml.) was then added to the clear, amber tetrahydrofuran solution. This solution was cooled to 0° for several hours, and the title product separated from solution as an off white powder in a crude yield of 71% (2.9g). The analytical sample (Table 14)was recrystallized from tetrahydrofuran (charcoal)-ether at -20° and was obtained as a white powder in 57% yield (2.3g). The melting point behavior of this product was peculiar. At 87.0-87.5° a nearly instantaneous surface wetting was noted. No additional change was noted until a sharp melt to a clear liquid was observed at 117-118°. The proton spectrum for this white solid is reproduced in Figure 52.

6-(2,2,2-Trifluoroethoxy)-4-(5-isopropylaminopentylamino)-1,5-naphthyridine (NT-8)

A mixture of 4-chloro-6-(2,2,2-trifluoroethoxy)-1,5-naphthyridine (3.0g, 11.4 mmole, NI-13), 5-isopropylaminopentylamine (10.0g, 13), and copper-bronze (0.5g) was slowly heated to 180-190° and maintained at that temperature for eighteen hours with the aid of an external oil bath. The resultant brown suspension was cooled to room temperature, and 50 ml. of 5 N sodium hydroxide added under strong stirring. The organic phase was then separated and combined with three-50 ml. ether extracts of the water layer.

After drying ($MgSO_4$), the ether was removed under a nitrogen purge to afford a brownish-orange liquid. This liquid was then subjected to molecular distillation. The excess diamine was removed over the range 25-155° (0.04 mm). Analytically pure product (Table 7) was subsequently obtained as a yellow-orange oil in 45% yield (1.9g, 155-165°/0.04 mm, n_D^{22} 1.5287). The proton spectrum, Figure 20, is clearly in accord with the formulated structure.

6-(2,2,2-Trifluoroethoxy)-4-(5-isopropylaminopentylamino)-1,5-naphthyridine di-β-resorcylate (NT-9)

Analytically pure 6-(2,2,2-trifluoroethoxy)-4-(5-isopropylaminopentylamino)-1,5-naphthyridine (1.30g, 3.52 mmole, NT-8) was dissolved in 50 ml. of ether at room temperature. A solution of 2,4-dihydroxybenzoic acid (1.11g of 97% purity, 2.0 mole-eq.) in 20 ml. of diethyl ether was then added dropwise. A white suspension formed immediately upon the addition of the acid solution. The suspension was then stirred an additional two hours at 25° before filtering under a nitrogen atmosphere. The solid was then immediately transferred to a vacuum oven and was dried at room temperature. The title salt was thereby obtained as a white powder in 81% yield (1.90g, m.p. 106-109°). The analytical data are included in Table 7, and the infrared spectrum is reproduced in Figure 21.

6-(2,2,2-Trifluoroethoxy)-4-(4-diethylamino-1-methylbutylamino)-1,5-naphthyridine di-β-resorcylate mono-hydrate (NT-10)

A sample of our previously characterized 6-(2,2,2-trifluoroethoxy)-4-(4-diethylamino-1-methylbutylamino)-1,5-naphthyridine (1.4g, 3.64 mmole, NT-2) was dissolved in about 50 ml. of diethyl ether at room temperature. A solution of 2,4-dihydroxybenzoic acid (1.12g, 7.29 mmole) in 20 ml. of ether was then added dropwise at room temperature. A white suspension formed immediately. After stirring for several hours, the suspension was filtered under nitrogen. The powder proved to be mildly deliquescent and was therefore immediately transferred to a vacuum oven and dried at room temperature (0.10 mm) for 2 days. The title salt was obtained as a white powder in 81% yield (2.10g, m.p. 105-106°). The analytical data (Table 7) consistently revealed the presence of one molecule of water of recrystallization.

6-Methoxy-4-(5-isopropylaminopentylamino)-1,5-naphthyridine (NT-11)

A mixture of 4-chloro-6-methoxy-1,5-naphthyridine (3.0g, 15.4 mmole, NI-28), potassium carbonate (2.2g, 16.0 mmole), and an excess of 5-isopropylaminopentylamine (10.0g, 69.5 mmole, 13) was slowly brought to 150° with efficient stirring. After eighteen hours, the brown suspension was cooled, 50 ml. of ether added, and the inorganic salt was removed by filtration. The ether layer was then shaken well with 50 ml. of 5N sodium hydroxide solution. The ether layer was then separated, combined with two additional ether extracts (50 ml), dried over magnesium sulfate, and the

ether removed under a nitrogen purge. The residual brown liquid was then subjected to a molecular distillation. After the diamine was removed, the title product was obtained as a yellow-amber oil in 64% yield (3.0g, 140-145°/0.01 mm, n_D^{27} 1.5582). The analytical data for this material are reproduced in Table 9, and the proton spectrum is reproduced in Figure 30.

6-Ethoxy-4-(5-isopropylaminopentylamino)-1,5-naphthyridine (NT-12)

A mixture of 4-chloro-6-ethoxy-1,5-naphthyridine (3.0g, 14.4 mmole, NI-29), potassium carbonate (2.1g, 15.2 mmole), and an excess of 5-isopropylaminopentylamine (10.0g, 69.5 mmole) was maintained at 150-160° for eighteen hours with the aid of an external oil bath. After cooling the amber suspension to room temperature, 50 ml. of ether was added and the inorganic salt was removed by filtration. The filtrate was shaken well with 50 ml. of 5N sodium hydroxide solution. The organic phase was then separated and combined with two ether washings (25 ml) of the water layer. The ether solutions were then dried over magnesium sulfate, and the solvent removed under a nitrogen purge. The residual amber liquid was then fractionated in a molecular distillation apparatus. After removal of the excess diamine, the title material was isolated as a yellow-amber oil in 53% yield (2.4g, 160-175°/0.04 mm; considerable bumping, most distilled at 160-165°/0.04 mm). The analytical data for this product are included in Table 9, and the proton spectrum is reproduced in Figure 31.

6-Methoxy-4-(5-isopropylaminopentylamino)-1,5-naphthyridine di-β-resorcylate (NT-13)

A slight excess of 2,4-dihydroxybenzoic acid (1.75g, 11.3 mmole) in 100 ml. of ether was added dropwise into the solution of 6-methoxy-4-(5-isopropylaminopentylamino)-1,5-naphthyridine (1.37g, 4.53 mmole, NT-11) at room temperature. A white suspension formed immediately as the addition progressed. After stirring for one hour, the suspension was filtered to afford the di-β-resorcylate salt in 82% yield (2.3g, m.p. 103-105°). The analytical data are included in Table 9, and the infrared spectrum is reproduced in Figure 32.

6-Ethoxy-4-(5-isopropylaminopentylamino)-1,5-naphthyridine di-β-resorcylate (NT-14)

A solution of 2,4-dihydroxybenzoic acid (1.57g, 10.2 mmole) in 50 ml. of ether was slowly added dropwise into a well-stirred solution of 6-ethoxy-4-(5-isopropylaminopentylamino)-1,5-naphthyridine (1.3g, 4.12 mmole, NT-12) in about 100 ml. of ether at 25°. After stirring for several hours, the suspension was filtered to afford the title product as a white powder in 79% yield after drying at 50° (2.1g, m.p. 96-98°). The analytical data for this product are included in Table 9.

6-Methoxy-4-(4-diethylamino-1-methylbutylamino)-1,5-naphthyridine (NT-15)

A mixture of preformed 4-chloro-6-methoxy-1,5-naphthyridine (2.6g, 13.3 mmole), potassium carbonate (2.0g, 14.5 mmole) and an excess of 2-amino-4-diethylaminopentane (20g) was slowly brought to 160° and maintained at this temperature for eighteen hours with efficient stirring. The resultant dark brown suspension was cooled to room temperature and 50 ml. of 5N sodium hydroxide added. After this extraction, the ether phase was combined with two additional ether extracts. It should be mentioned that an emulsion formed in the initial extraction step; however, this emulsion was easily broken by the addition of ca., 50 ml. of water. The combined ether extracts were dried over magnesium sulfate before the removal of solvent with a nitrogen purge. The residual brown liquid was then fractionated through a molecular distillation apparatus. Excess diamine was first removed at ca., 35-100°. Considerable sublimation of unreacted starting material was then noted near 100°. The title product was then collected as an amber oil in 36% yield (1.5g, 125-130°/0.07 mm, n_D^{25} 1.5468). The analytical data are included in Table 9, and the proton spectrum is reproduced in Figure 33.

6-Methoxy-4-(4-diethylamino-1-methylbutylamino)-1,5-naphthyridine di-β-resorcylate mono-hydrate (NT-16)

An excess of 2,4-dihydroxybenzoic acid (0.88g, 5.7 mmole) in 25 ml. of ether was slowly added dropwise into a solution of preformed 6-methoxy-4-(4-diethylamino-1-methylbutylamino)-1,5-naphthyridine (0.60g, 1.9 mmole, NT-15) in 50 ml of ether at room temperature. The resultant white suspension was stirred for several hours before filtering off the title salt in 50% yield (0.60g, m.p. 98-100). The analytical data (Table 9) consistantly revealed the presence of a mono-hydrate. The infrared spectrum for this white powder is reproduced in Figure 35.

3-Carbomethoxy-4-hydroxy-6-methoxy-1,5-naphthyridine (NT-17)

Recrystallized dimethyl 6-methoxy-3-pyridylaminomethylenemalonate (5.0g, 18.8 mmole, NP-28) was slowly added portionwise into refluxing diphenyl ether (50g). Heating was then continued for only a short period until a noticeable darkening of the reaction mixture occurred. After cooling to room temperature, the suspension was filtered and the crude product was obtained in quantitative yield (4.5g) after washing well with heptane. The analytically pure material (Table 10) was obtained in 57% yield (2.5g, m.p. 288-290°) after trituration with hot ethanol and drying at 110°. The infrared spectrum of this off white solid is reproduced in Figure 37.

6-Ethoxy-4-(4-diethylamino-1-methylbutylamino)-1,5-naphthyridine (NT-18)

A mixture of our previously characterized 4-chloro-6-ethoxy-1,5-naphthyridine (1.50g, 7.18 mmole, NI-29), 2-amino-4-diethylaminopentane (15.0g, 94.5 mmole), and a catalytic quantity of copper-bronze (0.5g) was slowly brought to 150° with efficient stirring. Heating was continued for a total of eighteen hours, at which point the dark brown solution was cooled to room temperature. Aqueous sodium hydroxide solution (50 ml of 5N) was then added with stirring to neutralize the hydrochloric acid generated in the reaction. The upper oily phase was then extracted into ether (3x75 ml.). The combined ether layers were dried over magnesium sulfate and the solvent removed to afford a brown liquid. This residual liquid was then subjected to molecular distillation. After removal of excess diamine the title product was collected as an amber oil in 67% yield (1.6g, 130-150°/0.05 mm). The analytical data are included in Table 9, and the proton spectrum is reproduced in Figure 34.

6-Ethoxy-4-(4-diethylamino-1-methylbutylamino)-1,5-naphthyridine di-β-resorcylate (NT-19)

A solution of 2,4-dihydroxybenzoic acid (0.70g, 4.55 mmole, 2.5 mole-eq.) in 100 ml. of ether was slowly added dropwise into a solution of preformed 6-ethoxy-4-(4-diethylamino-1-methylbutylamino)-1,5-naphthyridine (0.60g, 1.82 mmole, NT-18) in 100 ml. of ether at room temperature. A suspension immediately formed which was stirred for an additional several hours at room temperature. The title product was then isolated as a white powder in 95% yield by filtration under nitrogen (1.10g, m.p., 90-93°). The analytical data are included in Table 9.

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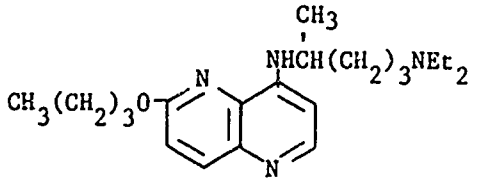
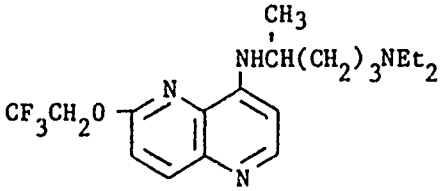
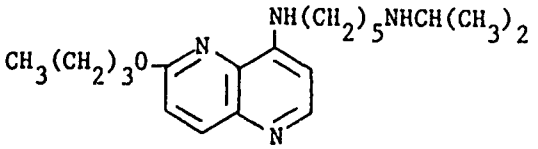
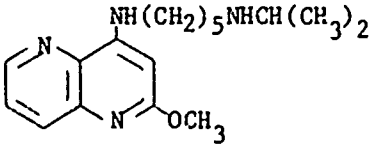
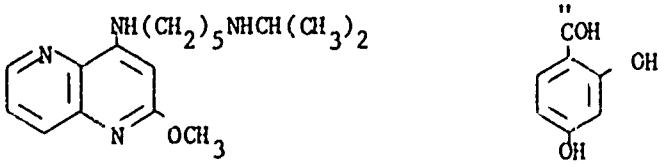
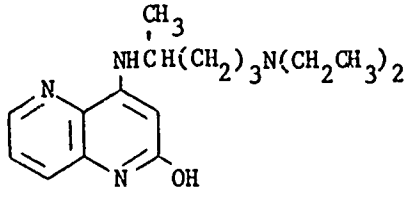
6. APPENDICES

6.1 Numerical Listing of Compounds Submitted

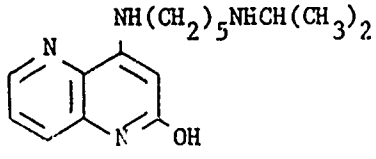
Below are listed the chemical structures and our code designation for each of the compounds which have been submitted for biologic testing this year.

Naphthyridine Targets (NT-1 through NT-19)

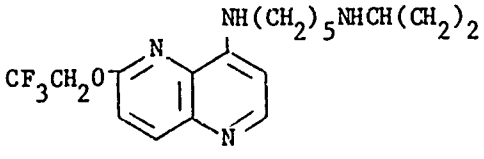
Structure	Code No.
	NT-1
	NT-2
	NT-3
	NT-4
	NT-5



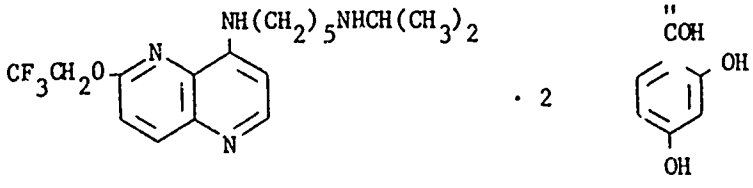
NT-6



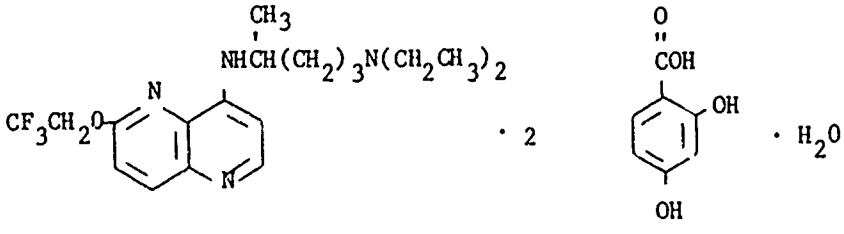
NT-7



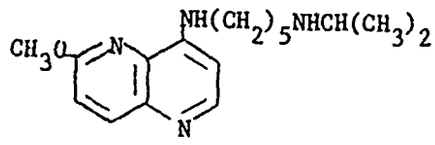
NT-8



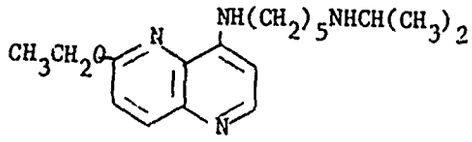
NT-9



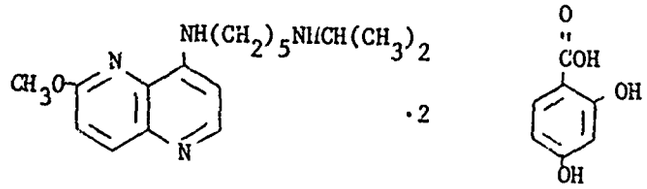
NT-10



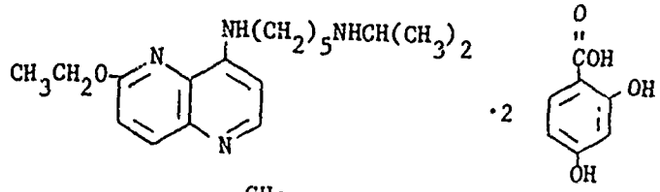
NT-11



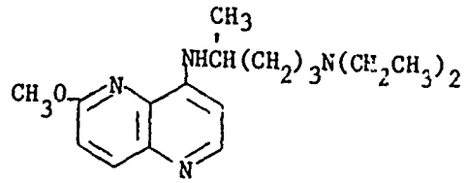
NT-12



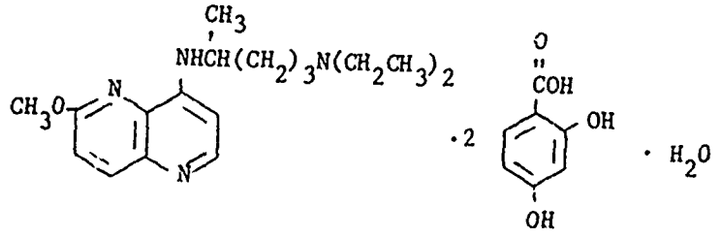
NT-13



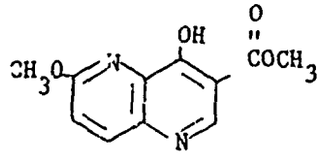
NT-14



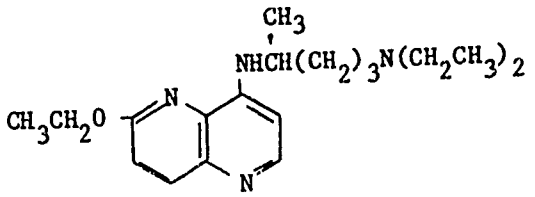
NT-15



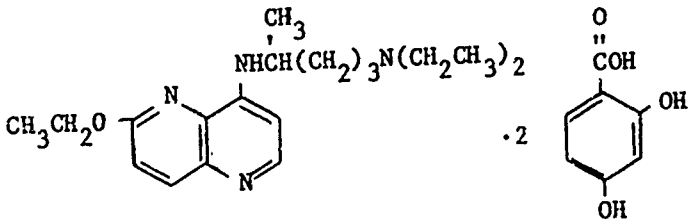
NT-16



NT-17

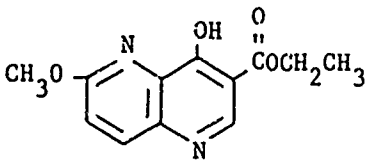
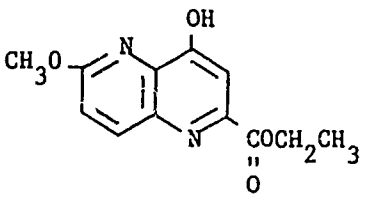
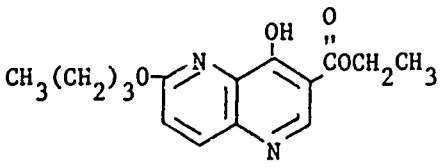
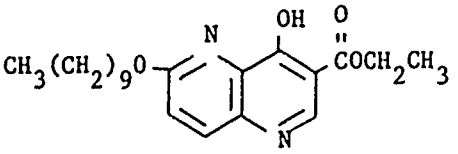
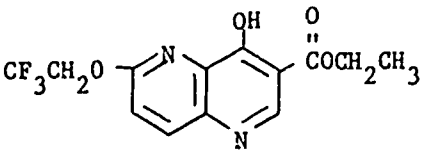
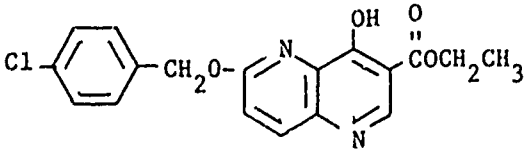


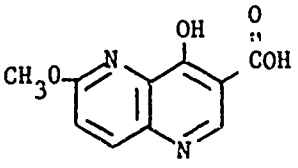
NT-18



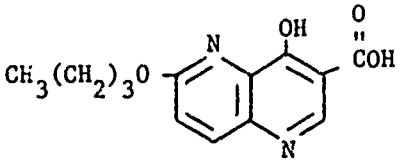
NT-19

Naphthyridine Intermediates (NI-1 through NI-41)

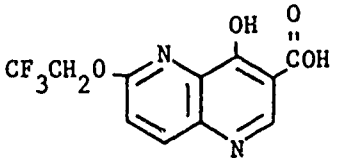
Structure	Code No.
	NI-1
	NI-2
	NI-3
	NI-4
	NI-5
	NI-6



NI-7

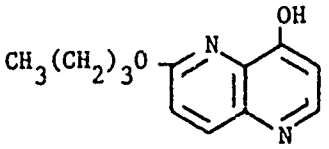


NI-8

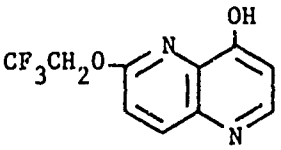


H_2O

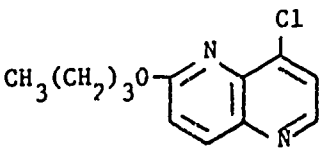
NI-9



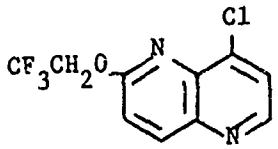
NI-10



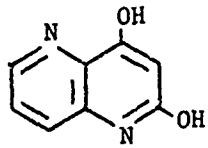
NI-11



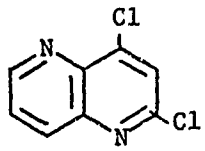
NI-12



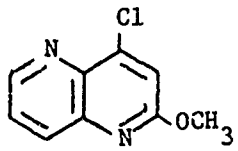
NI-13



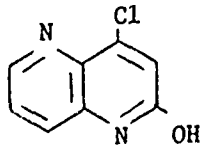
NI-14



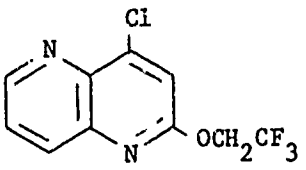
NI-15



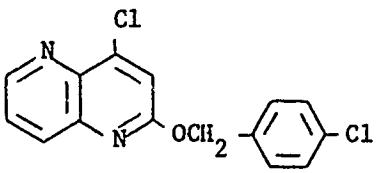
NI-16



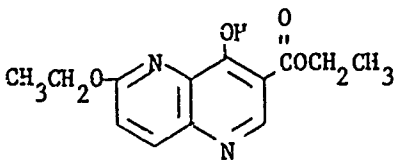
NI-17



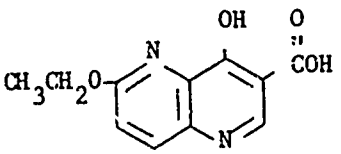
NI-18



NI-19

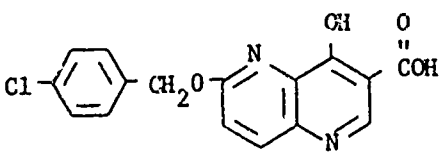


NI-20

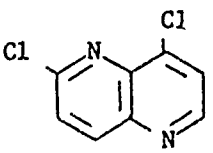


· 1/2 H_2O

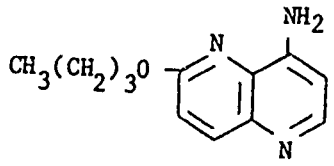
NI-21



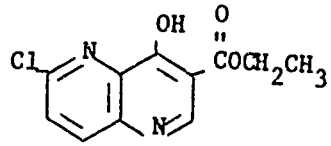
NI-22



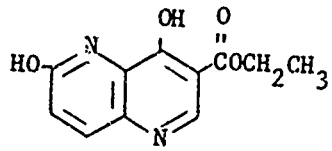
NI-23



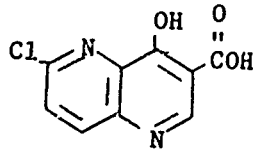
NI-24



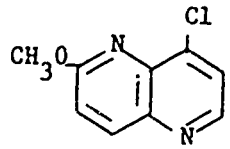
NI-25



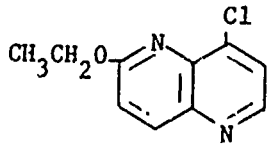
NI-26



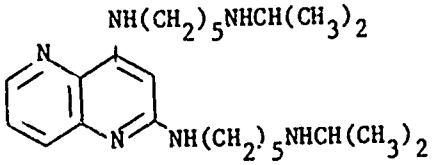
NI-27



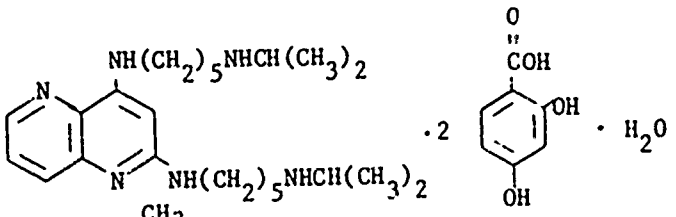
NI-28



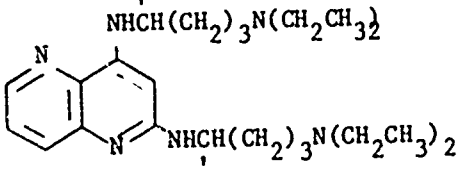
NI-29



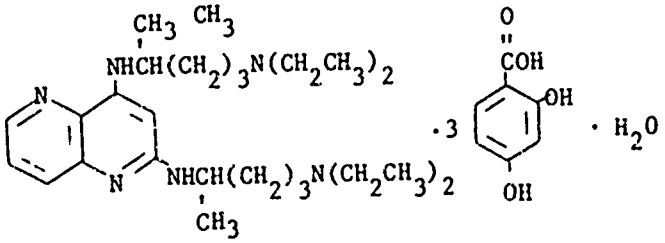
NI-30



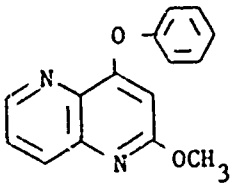
NI-31



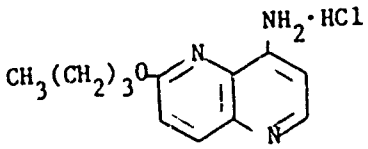
NI-32



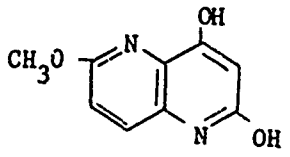
NI-33



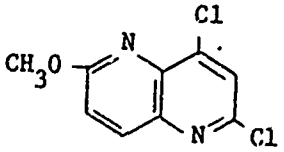
NI-34



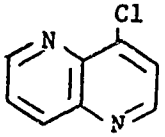
NI-35



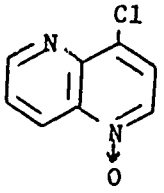
NI-36



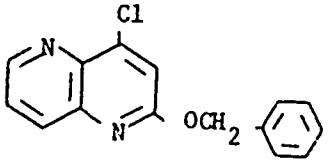
NI-37



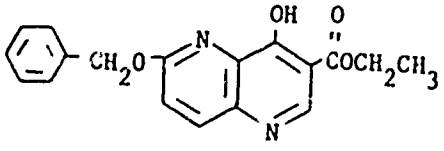
NI-38



NI-39

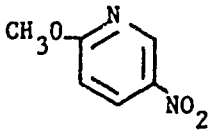
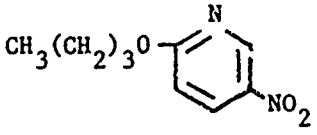
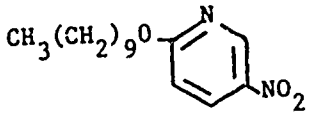
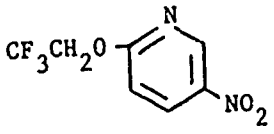
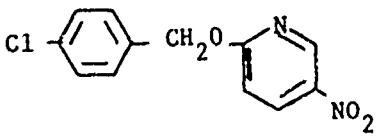
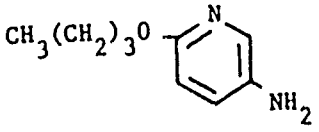


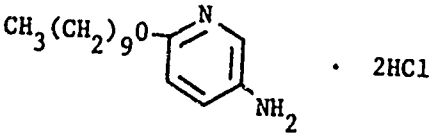
NI-40



NI-41

Naphthyridine Precursors (NP-1 through NP-43)

Structure	Code No.
	NP-1
	NP-2
	NP-3
	NP-4
	NP-5
 2HCl	NP-6



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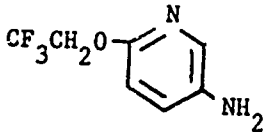

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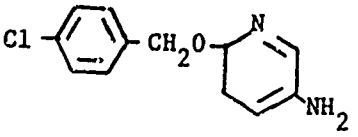

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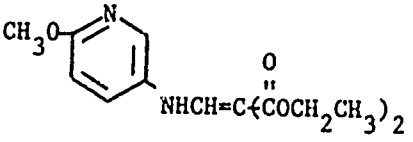

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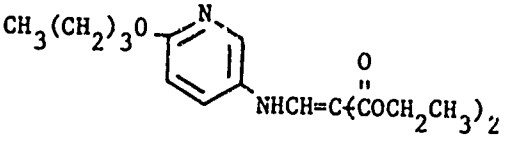

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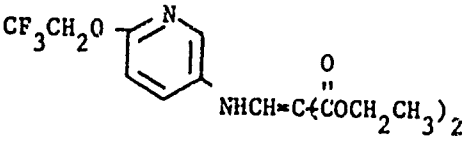

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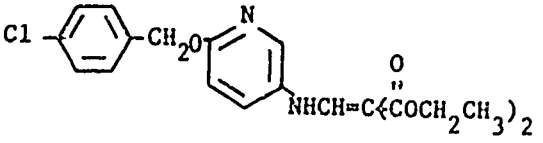

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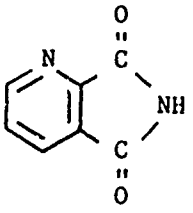

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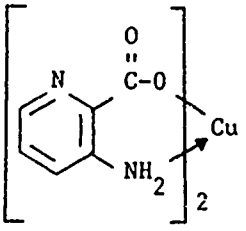

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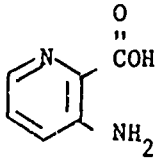

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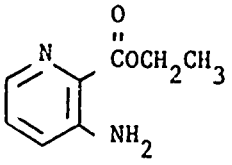

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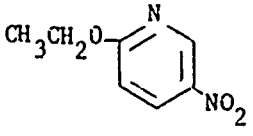

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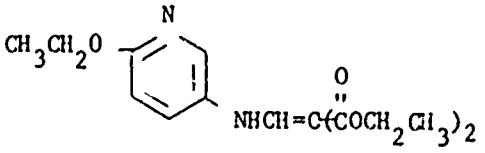

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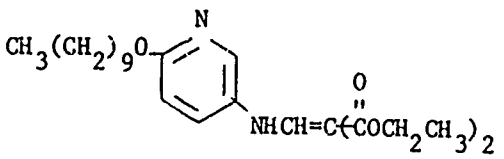

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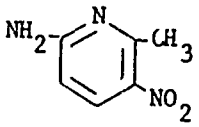

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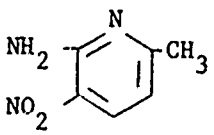

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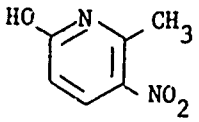

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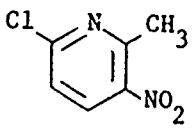

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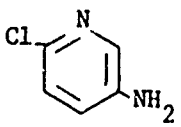

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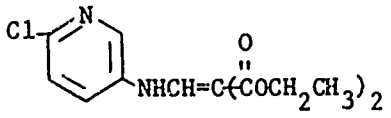

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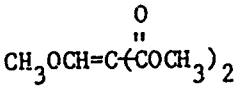

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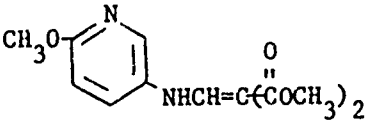

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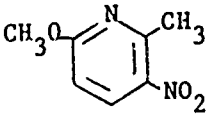

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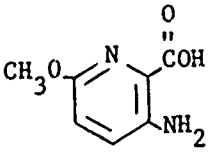

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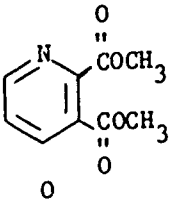

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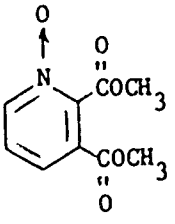

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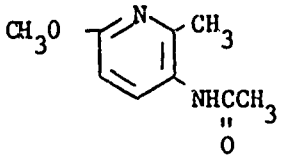

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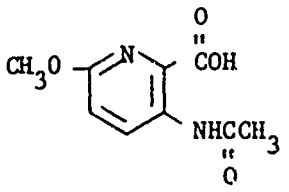

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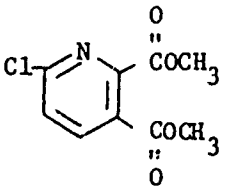

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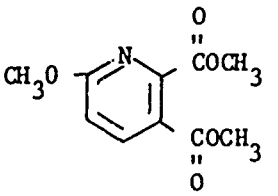

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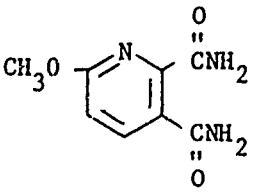

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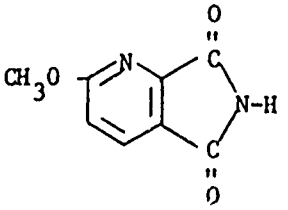

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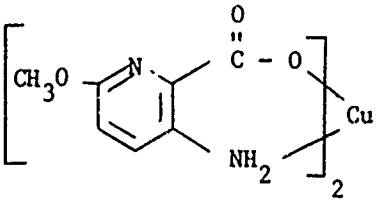

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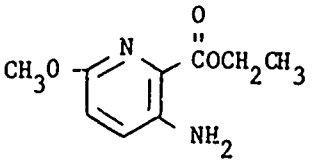

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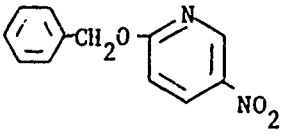

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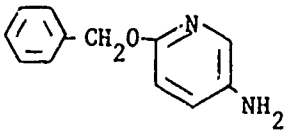

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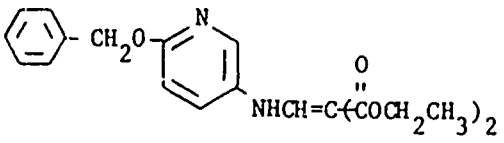
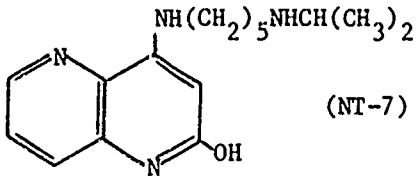


NP-43

6.2 Biological Activity Data

Test results for the prophylactic screen have been obtained for most of the target drugs which have been submitted to WRAIR. In general, no significant prophylactic activity has been observed in the Rhesus monkey in the lower dosage range (1 mg/kg). However, one target compound, 2-hydroxy-4-(5-isopropylaminopentylamino)-1,5-naphthyridine (NT-7), continues to afford protection after more than seventy days at a dosage level of 10 mg/kg.



(NT-7)

While biologic testing data are not yet complete in the therapeutic screen, we have included below a summary of the activity data received to date.

Compound		Activity (T-C)				
Code No.	WRAIR No.	40 mg	80	160	320	640
NT-2	BD26413	1.2	2.8	5.2	9.2	
NT-4	BD54711	0.1	0.3		0.9(4)	
NT-5	BD54720	0.1		0.1		0.1
NT-6	BD54739	0.1		0.1		0.3
NT-8	BD54757	2.9	3.7	5.9	7.9	
NT-9	BD54766	0.5	2.1	4.1	6.9	8.9
NT-10	BD54775	0.1		0.1		0.3

6.3 Program Organization and Personnel

This program has been conducted in the Government Research Laboratory of Exxon Research and Engineering Company. The prinicpal investigator for this project is Dr. John F. Pilot. During the first year of this program Dr. Pilot has been assisted by Mr. James H. Ballentine. Dr. Pilot is currently being assisted by Mr. Nelson C. Edwards. Dr. Daniel Grafstein, Manager of the Applied Science Section, has been responisble for the administrative aspects of this program.

6.4 Distribution Statement

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